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Overview on impact of PET at the general public level

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Abstract.

Diagnostidc imaging using X rays, radioisotopes (RI), nuclear magnetic resonance (NMR/MRI) and ultrasound (US) are now inevitable tools in medical diagnosis of diseases. Among them use of RI and radiopharmaceuticals has a unique features, in that images represent physiological and biochemical functions of organs, tissues and lesions. This modality that is the medical application of radio-tracer technology is called "Nuclear Medicine" and has nearly 100 years of histroy. Positorn emmission tomograpy or PET is a relatively new technology in nuclear medicine developed in the late 1970's.The regional phenomenon inside the body such as perfusion, metabolism and molecular dynamics can be invetigated using PET without giving any pain to patients (non-invasively). Therefore, it has contributed a lot to the recent progress of biomedical sciences by elucidating functions of the human brain, heart, and whole body. Clinical use of PET started to atract interest in the middle of 1980's, which became increasingly prevalent in developed countries in the past decade and in these several years in particular, by the common use of fusion images of PET and CT (PET/CT). Now PET has been used as routine clinical procedures for diagnosis of cancer, epilpsy and ischemic heart disease, as will be demonstrated in the representative cases.

The development of PET/CT machine allows simultaneous imaging of PET and CT in the same position which enables precise fusion of images of function with that of anatomy. In addition reconstruction of whole body images from trans-axial body tomographies allows the evaluation of the original lesion and metastasis of cancer using F-18-fluoro-deoxy glucose (FDG) as an indicator of increased glucose metabolism in cancer tissues.

By the approval of FDG PET as a procedure to be reimbursed by the national health insurance system (NHIS) in Japan as well as delivery of FDG by a radiopharmaceutical company, clinical PET facilitaies has rapidly increased in the recent several years to reach nealy 200 with over 300 PET or PET/CT being used. In Japan PET/CT procedures have freaquently been used outside of NHIS to be applied to health checkup of healthy subjects, mainly cancer screening purpose. This trend reflects the increasing societal interest towards preventive medicine. It is expected that some invasive technologies may be avoided by the introduction of PET/CT. Large scale PET imaging centres such as with 10 PET scanners and 2 cyclotrons are operated. For the production and delivery of FDG to cover all over Japan 9 branch factories with cyclotrons and automated synthesis and labeling systems were constructed by a radiopharmaceutical company. Obviously this trend has stimulated related industries.

Radiation protection of workers is another important issue when PET and PET/CT became so popular. Training of PET/CT specialists is also an urgent problem to solve in order to maintain high quality of image interpretation. Prevailing use of PET/CT will change the practice and education of diagnostic imaging, in that PET/nuclear medicine specialists cooperate with CT/diagnotic radiology specialists.

Although FDG PET is a useful tool of cancer detection as widely recognized among the general public in Japan, FDG is not necessarily the ideal tracer for cancer detection. The efforts have to be made to develop better radioharmaceuticals. Oncology is not the only field PET can contribute, either. It will play important roles in clinical neurology and psychiatry not to mention in cardilogy in near future. Progress of molecular biology and nanotechnolgy has reached the phase that seeks for their clinical aplications. PET is one of the most advanced and promising tool at present to trace the gene expression and dynamics of protein and other molecules in human. And thus it will contribute clinically to gene therapy and regenerative medicine by providing better management of patients in

diagnosis, treatment planning and evaluation of treatment effects. Continuous research is needed to improve the current technology of PET and fusion images in order to provide better medical care to patients. This aspect should be emphasized by specialists to be understood by the general public.

After 40 years since development of PET it became a clinically important instrument in every day medical practice. Promotion of the use of PET/CT in Asian countries is still necessaray at this stage for the sake of patients. I understand this conference is one of those activities implimented by IAEA. The Forum for Nuclear Cooperation in Asia (FNCA) supported by the Atomic Energy Commission of Japan has also been making efforts to support medical use of radiation and radioisotopes in Asia. The promotion of PET is an example.

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PET ONCOLOGY I

Lung cancer

P. Conti

Value of PET and PET-CT in the management of lymphoma

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Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) is now widely used for staging and monitoring treatment results in patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Together, HD and NHL comprise only 8% of all malignancies, but most patients are young and potentially curable. In contrast to many solid tumors, lymphomas are highly sensitive to chemotherapy or radiotherapy and substantial long-term cure-rates of 90% for HD and 50% for aggressive NHL are expected with the current treatment options. However, the magnitude of late treatment-related morbidity and mortality especially in young HD patients treated with combination chemo-radiotherapy as well as the fact that still a considerable amount of NHL patients cannot be cured with standard induction therapy, has tempered the initial enthusiasm. Accordingly, tailoring the intensity of the treatment to individual patient basis has become very important. There are 3 principal domains to optimize the management of lymphoma patients in which FDG-PET has potential advantages: improving the accuracy of initial staging, early and more accurate assessment of response to treatment and finally optimizing the follow-up after therapy. In this lecture, the value of PET in these different areas is discussed.

Several studies have investigated the role of FDG-PET for the **initial staging** of lymphoma. The majority of the studies compared the performances of PET with other imaging modalities. Studies were often retrospective and included a mix of NHL and HD without separate analysis for both subgroups. Another drawback is the missing of a true gold standard since discordant findings were rarely histological confirmed. In a recent meta-analysis [1] which included 20 studies, the pooled sensitivity was 90.9% and the pooled false-positive rate was 10.3%. Most reports focused on the comparison of PET with CT. PET was found to be more sensitive in both the detection of nodal (e.g. small sized nodes) and extra-nodal (especially spleen and bone involvement) disease, but PET negative, CT positive lesions do occur in a small number of cases. High FDG uptake in brown fat tissue or muscle can hamper the interpretation of the head & neck and mediastinal region and physiological uptake in the brain, myocardium and renal collecting system can obscure lymphoma evaluation in those sites. Therefore, FDG-PET should not be used in stead, but in combination with CT. Especially the use of combined PET-CT machines can improve the accuracy by increasing the certainty of diagnosis in those difficult regions.. Improved lesion detection and characterization led to a modification of disease stage and subsequent management in only a limited number of patients and the impact on outcome remains unknown. The most important reason to perform a baseline PET scan is to facilitate the evaluation of residual disease after therapy, currently the most established indication for PET in lymphoma.

At the **end of treatment,** lymphoma patients often present with a residual mass but only a minority of them will eventually relapse. Structural imaging can not reliably discriminate fibrotic from viable tumor masses. Early identification of patients who have not been cured by their primary treatment is however important since better outcome after further treatment can be expected when such patients are treated at an earlier stage with lower tumour burden. Numerous studies have shown the effectiveness of FDG-PET in the detection of residual disease at the end of therapy. In a recent systematic review [2] including 15 studies (350 NHL and 408 HD), the pooled sensitivity and specificity for detection of residual disease in HD were 84% and 90%, where for NHL this was 72% and 100%. A negative PET at the end of treatment clearly identifies patients with an excellent prognosis. Relapses are infrequent and occur rarely within the first year after the end of treatment probably reflecting minimal tumor burden below the detection limit of the PET system at the time of restaging. Since a substantial number of patients still received additional RT after a negative PET scan especially in HD, reported negative predictive value and progression free survival can be overestimated. A positive PET is

associated with a high probability of relapse but since increased FDG uptake can also be seen in inflammation and some normal structures (muscle, brown fat), a close correlation with clinical data, other imaging modalities and/or biopsy is mandatory before starting salvage treatment. The increased use of combined PET-CT scanners resulted in the formulation of new response criteria including both PET and CT results [3,4]. Promising data indicate that FDG-PET after a few cycles of chemotherapy is an important **prognostic factor**. Persistent abnormal FDG uptake at interim PET probably reflecting deposits of chemoresistant cell clones, is associated with a short progression-free survival. However, no published reports have yet demonstrated that PET-response-adapted therapy also improves outcome. Finally, only limited data are available on the use of PET in **the follow-up** of asymptomatic patients. The high rate of false positive findings and the lack of evidence that early detection of recurrence also improves overall survival, warrants further studies before this can be implemented in routine clinical practice.

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Melanoma

H.A. Macapinlac

PET-CT for evaluation of chemotherapy response in patients with high-grade lymphomas

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Background: Positron emission tomography using F18-flourodeoxyglucose (FDG-PET) is considered an excellent tool for staging, restaging and monitoring disease status in patients with high-grade lymphoma. Evaluation of chemotherapy response is an important aspect for the management of these patients, which can be assessed by clinical, imaging and histopathological criteria. Evaluation of chemotherapy response is important in tailoring the intensity of the treatment and predicting recurrence of disease. Decrease in size of lymphomatous mass in post-treatment CT/MRI when compared with pretreatment CT/MRI scan is considered as response to treatment. However, this decrease in size may take a long time or may not occur in cases of fibrosis and necrosis. These residual masses represent up to 85% of patients treated for Hodgkin disease (HD) and up to 40% of those treated for non-Hodgkin lymphoma (NHL) [1,2]. Recent studies have demonstrated use of PET in treatment evaluation [3,4]. However, PET alone has problem of exact localization. The **aim** of this study was to assess the role of FDG- PET/CT in the evaluation of response to therapy in patients with HD and NHL.

Materials and Methods: Fifty-two patients of lymphoma (25 HD, 27 NHL) with mean age of 43.2 years (age range 14-76 years), (32 male, 20 female) were included in this study. Forty of 52 patients had only nodal disease whereas 12 had disease at extra nodal sites in addition to nodal disease. All patients were fasted for 4 hours prior to the PET-CT scan. PET-CT imaging was performed using a dedicated whole body PET-CT scanner (Biograph, Siemens). Scanning was done at approximately 60 minutes after FDG injection of about 10 mCi. After image reconstruction, a region of interest (ROI) was carefully drawn around the site of the abnormal FDG uptake in the consequent 4-6 PET-CT scan slices. The slice with a maximal FDG uptake in the ROI was chosen for quantitative measurement of metabolic activity of the tracer (SUV). Both average and maximum SUV values were calculated for each ROI. All patients underwent a baseline PET-CT scan (pre-chemotherapy) and follow-up PET-CT scan (post- chemotherapy). Follow-up scan was done 2 weeks to 5 months after completion of last cycle of chemotherapy. Both the PET-CT studies were analysed (qualitatively and semi-quantitatively) and compared for any change in FDG uptake.

Results: After the completion of treatment, complete resolution of the disease was seen in 33 (19 HD, 14 NHL) patients, partial resolution in 12 (6HD, 6 NHL) and no improvement or deterioration in 7 (all NHL) patients. There was good correlation of PET-CT findings with clinical assessment in all patients. All the 19 patients with partial or no improvement underwent more aggressive therapy. Six of these 19 showed complete resolution in follow-up scan. Two patients were found to be false positive. In addition, 9 patients showed parenchymal inflammatory/infective lesion in the both the lungs, which were not seen in the pre chemotherapy, scans. These lesions could be attributed to an inflammatory/infective disease process as a result of chemotherapy-induced reduction in immune status, as these were not seen in the pre chemotherapy scans.

Discussion: Evaluation of the treatment response is an important aspect in the management of lymphomas. However, residual masses are frequently observed after treatment, and CT is often unable to discriminate between vital tumor and inactive fibrotic tissue [4]. Till recently, gallium scintigraphy was playing an important role in clarifying the CT detected residual masses. However, it has limitation of limited resolution and non-specific uptake in benign lesions. PET has been recommended for differentiation between viable residual tumor or recurrent tumor and scar tissue after tumor therapy [3,4]. PET may provide superior information for clinical management by enabling biochemical tissue

characterization, namely, with high 18F-FDG uptake in viable post therapeutic lymphoma masses and very low uptake in indolent fibrotic tissue. The diagnostic accuracy of PET for assessing the presence of residual disease after therapy is superior to that of CT [3,4]. A positive PET scan after the end of therapy in HD patients is a strong predictor of relapse. On the other hand, a negative PET scan after the completion of therapy can provide very favorable prognostic information but does not exclude the presence of residual microscopic disease.

Conclusion: PET-CT play important role in the assessment of response of treatment in patients with high-grade lymphoma. A negative study is associated with disease-free period not requiring further therapy, even when residual mass is detected on CT. A positive PET-CT scans after the completion of therapy is a strong predictor of residual/recurrent disease in patients with HD and NHL. The diagnostic accuracy of PET-CT scans is superior to CT scans in evaluating the presence of residual disease after the end of treatment. Identification of patients with suboptimal response with PET-CT may substantially influence future treatment strategies in such clinical settings.

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Evaluation of pulmonary tumors with ^{18}F-FDG PET/CT

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Background: Correct characterization of pulmonary lesions remains a difficult task for clinicians. Adequate management of these lesions relies on the correct diagnosis of the primary lesion and of potential secondary locations, which allows curative resection of early-stage malignant nodules and avoids the morbidity and mortality of surgery for benign ones or for patients with demonstrated distant metastases, which would probably benefit more from radiotherapy and/or chemotherapy. Conventional imaging techniques used for the study of lung tumors have a very high sensitivity of up to 98% for contrast enhance helical CT, but a limited specificity of 58% for the diagnosis of malignant pulmonary nodules. Over the past several years, ^{18}FDG PET has become an additional option in the evaluation of patients with lung tumors and has led to changes in the work-up of indeterminate pulmonary nodules. Numerous studies have shown PET to be effective in the differentiation of benign from malignant lesions, with an overall sensitivity of 96% (range, 83%–100%), specificity of 79% (range, 52%–100%), and accuracy of 91% (range, 86%–100%). However, it is well established that PET sensitivity is worse for small lesions (less than 1 cm) and for some specific malignant lesions with reduced metabolic activity (bronchioloalveolar carcinoma). On the other hand, various benign conditions may simulate hypermetabolic neoplasic lesions that can lead to false positive results in PET studies. Multimodality PET/CT technology benefits from both the metabolic information of provided by PET and the high anatomic resolution of CT, which, together, improve both sensitivity and specificity in the characterization of pulmonary tumors. In this report we describe our experience in the characterization of pulmonary tumors in Chilean population with ^{18}FDG-PET/CT.

Methods: 158 patients (92 males and 66 females) with solitary pulmonary tumors were prospectively included in the study, mean age 63.1 years (26-96). All patients had histopathological study and/or clinical and complementary imaging follow up longer than 6 months. 68 patients had nodules of less than 30 mm and 90 had masses between 31 and 120 mm. All the PET/CT scans were acquired in a Siemens Biograph 6 Hi-Rez system. PET images were acquired approximately 60 minutes after the injection of 10 mCi (370 MBq) of ^{18}FDG associated to a full diagnostic CT with IV contrast media injection. All patients had glucose plasma level <140 mg/dL. The “maximum standard uptake value” (SUV Max) was calculated in all hypermetabolic lesions. All the studies were read simultaneously by both qualified nuclear medicine physicians and radiologists. Lesions were classified as malignant, benign and indeterminate, based on both radiological appearance and metabolic activity in PET/CT, with no SUV Max cutoff to distinguish one from another, but an integrated diagnostic criteria. For this reason, some lesions that were classified as malignant could have SUV < 2.5 g/ml, and some hypermetabolic lesions with SUV Max > 2.5 g/ml could be considered benign.

Results: According to our PET/CT criteria 115 patients (72.8%) were classified as malignant, 31 (19.6%) as benign and 12 (7.6%) as indeterminate. Malignancy was demonstrated in 109 of 115 patients categorized as malignant by PET/CT (94.8%); 6 false positive results were due to 4 infectious/inflammatory lesions and 2 benign carcinoid tumors. Within the true positive malignant lesions we found 6 small cell lung cancers (SCLC), 96 non small cell lung cancer (NSCLC) and 7 metastases. In the group with lesions considered benign for their anatomic and metabolic characteristics, 4 were demonstrated malignant by biopsy (12.9%), 2 metastases of colorectal cancer, 1 metastasis of thyroid cancer and 1 of angiosarcoma. In the indeterminate lesions group, 5 lesions resulted malignant (41.7%), 3 lung cancers, 1 metastasis of kidney cancer and 1 of colorectal cancer. Median SUV Max was 10.4 g/ml (1.8-35.9) in the malignant group, 1.0 g/ml (0.3-15.3) in the benign group, and 2.2 g/ml (0.6-5.3) in the indeterminate group. Difference on SUV of malignant and benign lesions was highly significant. Positive predictive value (PPV) for malignancy in the malignant group

was 94.8%. False negative results were found in 9 patients (7.6%), which corresponded to 41.7% of the indeterminate group and in the 12.9% of the benign group.

Conclusion: The data presented here show that using a combined PET/CT criteria ^{18}FDG PET/CT is a reliable method for the study of pulmonary lesions, with a 94.8% positive predictive value for malignancy and 87% of negative predictive value. Since within the small number of patients with indeterminate lesions 41.7% of malignancy was found, further analyzes, including, histopathological study are essential in this group.

PET ONCOLOGY II

PET/CT in colorectal and gastro-intestinal tumors

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Staging an restaging of colorectal cancer: The effectiveness of FDG PET/CT at initial diagnosis of colorectal cancer has been evaluated only by one study to date, but the usefulness of PET suggests that its use is indicated [1]. Two studies using FDG- PET alone for initial staging have demonstrated a high sensitivity in the detection of the primary tumor (100% and 96%) as well as distant metastases (87% and 78%) and a low sensitivity (29% and 29%) in lymph node staging [2,3].

Restaging of colorectal cancer: In the study by Seltzner et al., the diagnostic value of contrast-enhanced CT (ceCT) and non-enhanced PET/CT were prospectively evaluated against each other in 76 patients referred for preoperative evaluation for liver resection for metastatic colorectal cancer [4]. ceCT and PET/CT provided comparable findings for the detection of intra-hepatic metastases with a sensitivity of 95% and 91%, respectively. However, PET/CT was superior in establishing the diagnosis of intra-hepatic recurrence in patients with prior hepatectomy. Local recurrences at the primary colo-rectal resection site were detected by ceCT and PET/CT with a sensitivity of 53% and 93%, respectively. Extra-hepatic disease was missed in the ceCT in one-third of the cases, while PET/CT failed to detect extrahepatic lesions in only 11% of the cases. New findings on PET/CT resulted in a change in the therapeutic strategy in around 20% of the patients. To date, no data is available regarding the impact of intravenous contrast enhancement in PET/CT compared to non-enhanced PET/CT. Obviously only a limited incremental value can be expected since non-contrast PET/CT is already superior to ceCT.

Gastrointestinal stromal tumors (GIST): GIST are mesenchymal tumors that in approximately 90% of cases originate in the stomach and small intestine. In contrast to ceCT, FDG-PET is able to show early effects in patients undergoing treatment with imatinib mesylate [5]. In two recent studies it was shown that patients without FDG uptake after the start of treatment had a better prognosis than patients with residual activity which is not demonstrated with ceCT [6,7].

Primary liver tumors and pancreatic carcinoma: In patients with known moderately to poorly differentiated HCC, PET imaging has shown to be useful, particularly in the detection of distant metastases and follow-up after treatment [8,9]. In patients with extrahepatic cholangiocarcinoma (CC) and gallbladder-cancer, detection of unsuspected distant metastases changes the management in a considerable amount compared to conventional imaging studies including contrast-enhanced CT. Regarding locoregional metastases, FDG-PET/CT as well as ceCT has a rather low sensitivity [10]. In the evaluation of the pancreas, differentiation of pancreatic masses remains difficult with all imaging modalities. Heinrich et al. evaluated 59 patients with suspected pancreatic cancer, staged by abdominal CT, chest X ray and CA 19-9 measurement and FDG-PET/CT, and findings were confirmed by histology [11]. PET/CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging and demonstrated to be cost-effective. Despite its impact on the staging of pancreatic cancer, neither PET nor PET/CT can replace ceCT and endoscopic ultrasound.

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FDG PET in head & neck and thyroid cancers

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Head and neck cancer is one of the common carcinoma in human being, and incidence of thyroid cancer is increasing recently. FDG PET can be used in the preoperative detection and staging, monitoring therapeutic response and detecting/excluding recurrent cancer in head & neck and thyroid cancers.

For staging newly diagnosed head & neck cancer, PET has a comparable accuracy compared to CT, MRI and physical exam, but superior in lymph node staging. Assessing the response of primary head & neck cancers to chemotherapy or radiotherapy is feasible by PET. Follow-up of patients after surgery/radiotherapy and chemotherapy can be challenged using anatomical imaging methods due to alteration of normal structures. FDG PET is more accurate than MRI for the detection of recurrent tumors. Metastatic lesion distal to head & neck can be imaged clearly in one time with a whole-body PET. Interpretation of head & neck PET studies is somewhat difficult in that there can be considerable normal physiologic uptake of FDG. PET/CT can clarify physiologic uptake and pathologic uptake.

Although thyroid cancer has a higher FDG uptake than benign nodule, there is a partial overlap. The major role of FDG PET in thyroid cancer is in patients with elevated thyroglobulin levels where thyroid cancer tissues do not concentrate radioiodine. PET can fail to localize the tumor sites in some patients with well-differentiated thyroid carcinoma that retain good iodine ability. That can result “the flip-flop phenomenon” depending on the differentiation of the thyroid cancer. We also found that the expression level of sodium/iodide symporter was higher in well-differentiated carcinomas, while the expression level of glucose transporter-1 was lower in well-differentiated carcinoma than in less well-differentiated carcinoma. Incidental uptake of FDG is found in whole-body PET not infrequently, and malignancy occurs 1/3 to 1/2 of these cases. It is possible to use FDG PET as a prognostic marker in patients with thyroid cancer.

Besides FDG, positron emitter labeled amino acids, and thymidine have been developed as markers for amino acid metabolism or cell proliferation in head & neck and thyroid cancers. There seems to be a big potential role of PET in management of patients with head & neck or thyroid cancer.

Breast cancer

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PET in breast cancer patients has resulted in a great help for detecting malignant lesions and offers additional information in comparison to other conventional imaging modalities, such as ultrasonography (US), mammography, computed tomography (CT) and magnetic resonance (MRI). PET in breast cancer patients is based mainly on 2-deoxy-2-fluoro-D-glucose labelled with fluorine-18 (^{18}F-FDG). An impressive series of data confirms that FDG-PET plays a relevant role in the management of cancer. The evolution of PET instruments has made available new integrated PET/CT system, that combines a PET camera with a CT scanner in a single session, providing both anatomical and functional information at the same position. ^{18}F-FDG -PET/CT may improve the accuracy of cancer images, and the clinical experiences have demonstrated a diagnostic value superior than that of CT and PET alone. PET shows a good sensitivity in the diagnosis of primary carcinoma for tumours >0.8 cm and with a high probability of malignancy. For non palpable tumours or for smaller breast lesions the sensitivity and specificity are lower, due to the physical detection limits. The hybrid system PET/CT can increase the specificity of the test. In the literature there are reports of very small lesions shown by PET/CT; the hypermetabolism of cancer tissues becomes a positive factor for detection. In spite of such interesting results with PET and PET/CT, it is wordlwide accepted that FDG-PET should not be considered the first choice modality for the study of a breast mass. In this field mammography, associated with US, maintains a superior diagnostic efficacy with the advantage of a lower cost.

PET visualizes also loco-regional lymph nodes. FDG-PET has been extensively evaluated for staging axillary nodes, with a sensitivity ranging from 30% to 80% and a specificity from 70% to 100%. This variability is due to the different series studied and the various technical protocols. Some studies were carried out on patients who had FGD-PET and the pathological lymph node diagnosis. Considering the overall experience with FDG-PET in studying axillary lymph nodes, the detection of the small lesions mainly depends on PET resolution which for PET is around 5 mm. The SLNB after lymphoscintigraphy has shown a very higher sensitivity and has achieved a general consensus in staging axilla. A comparison between the SLNB and FDG-PET demonstrated that the sensitivity of FDG-PET resulted lower (40-60%); however the specificity and the positive predictive value are about 95% and 90% respectively. The high specificity of PET suggests that patients with a PET-positive axilla should have an axillary lymph node dissection rather than a sentinel node biopsy for axillary staging. In contrast FDG-PET has shown a poor sensitivity in the detection of axillary metastases, confirming the need for SLNB in cases where PET was negative for axilla.

FDG PET has a role in staging patients with locally advanced breast cancer. The addition of FDG-PET to the standard work-up of these patients can lead to the detection of unexpected metastases. This may contribute to a more realistic stratification between patients with true stage III breast cancer and those who are in fact at stage IV disease. FDG-PET in a group of patients with breast cancer at the diagnosis demonstrated distant metastases in 5% of them. Distant metastases were demonstrated in 30% of patients who were thought only to have local-regional recurrence. There is clear evidence the FDG-PET has a great value in tumour staging, since permits a complete tumour staging with a single whole body investigation, allowing the diagnosis of a significant number of metastases which would have been missed or non correctly diagnosed by CT, US, MRI and also bone scintigraphy.

FDG-PET and PET/CT have a role in following-up the patients with breast cancer. PET can be used on the asymptomatic patients with a high risk of recurrence (with poor prognostic factors) and the in the patients with symptoms where the detection of the sites and the extension of metastases is vital in order to plan a correct therapy.

PET-FDG is able to measure the metabolic changes in tissues. The metabolic response of the tumour proceeds the dimensionally measurable response, since the treatments primarily influence the metabolism and only later cause a decrease of tumour mass. The usefulness of PET in the evaluation of different therapies has been studied (chemotherapy, hormone therapy and radiotherapy). Histopatological response could be predicted with an accuracy around 90%. A semi-quantitative evaluation (through the Standardized Uptake Value, SUV) is a key-parameter used for therapy monitoring. This approach should be used both to check the efficacy of the therapy at the end of the treatment and also to measure the sub-clinical response of the tumour mass during the treatment, in order to predict the grade of clinical response. The FDG-PET study at the end of the treatment can be also an index of prognostic stratification for survival.

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The clinical significance of ^{18}F-FDG PET/CT on patients with nasopharyngeal carcinoma

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Aim/Background: Nasopharyngeal carcinoma (NPC) is a progressive head and neck malignancy prevalent in southern China and Southeast Asia. Accurate staging, and early detection of local recurrence and distant metastasis are key factors in selecting the most appropriate medical management. CT is routinely used in conventional work-up due to its ability to detect bone erosion, regional lymphadenopathy, and to screen for distant metastases. In terms of contribution to local T-staging, MRI is better than CT for displaying nasopharyngeal soft tissue and for differentiating tumor from soft tissue. MRI is also more sensitive for assessment of retropharyngeal and deep cervical nodal metastases [1]. However, both CT and MRI have limitations in the comprehensive assessment of NPC, particularly due to their reliance on nodal size for detecting disease [2]. In recent years, ^{18}F-FDG PET and PET/CT has proven to be an accurate functional imaging technique in the diagnosis, staging, restaging and therapeutic monitoring of many common cancers [3]. The aim of this study was to evaluate the accuracy and specificity of ^{18}F-FDG PET/CT on patients with NPC compared to the conventional work-up.

Methods and materials: Forty three patients with NPC were prospectively enrolled into an ongoing trial of the impact of PET/CT in clinical management. All had pre-PET staging and determination of management plan based on conventional imaging or clinical examination of the nasopharynx prior to the PET scan. There were 64 ^{18}F-FDG PET/CT scans altogether in this study, 18 were referred for staging, 20 for restaging and 26 for therapeutic monitoring or assessment after completion of therapy. Routine conventional work-up included CT, or MRI, or both. The final definitive diagnosis obtained from the medical record and pathologic reports, and clinical follow-up. The accuracy, specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of ^{18}F-FDG PET/CT and conventional work-up were calculated.

Results: The Accuracy, Sensitivity, Specificity, PPV, and NPV of ^{18}F-FDG PET/CT and conventional work-up were 95%, 100%, 86%, 93%, 100%, and 66%, 79%, 65%, 82%, 58% respectively. A primary thyroid cancer and a low grade gastric tumor were detected by ^{18}F-FDG PET/CT incidentally. ^{18}F-FDG PET/CT detected distant metastatic disease in 4 patients, which were not found on the conventional imaging. The PET/CT had demonstrated more lymph nodes than CT and MR in 5 patients. In one case, PET/CT correctly downstaged from T4N1 to T4N0. PET/CT had a direct impact on patient management in 33% (14/43) patients, and had a potential impact on another 33% (14/43) of patients.

Discussions: ^{18}F-FDG PET/CT was more accurate in the staging and restaging of NPC than conventional techniques and provided complementary information particularly with respect to regional nodal and systemic disease. Following treatment, the negative predictive value of ^{18}F-FDG PET/CT in cancer imaging was high with no patient relapsing during the follow-up period after a negative scan. Therefore, one can conclude that patients with suspected recurrence but negative PET/CT scan do not require active treatment although ongoing surveillance is probably prudent since residual microscopic disease could potentially be missed on PET/CT, particularly if this investigation is performed relatively soon after treatment. In contrast, positive predictive value and specificity are somewhat lower for local recurrence at or near the site of the primary tumor, related to a small number of false-

positive findings. Nevertheless, if used in a clinical algorithm, a positive PET scan requires a biopsy; if this biopsy is negative for recurrent cancer and does not provide reasons for a false-positive PET scan (inflammation, infection, radiation necrosis etc.), close clinical follow-up and potential repeat biopsy may be required.

Conclusion: ^{18}F-FDG PET/CT is better than conventional imaging in N、M staging and therapy monitoring of NPC. ^{18}F-FDG PET/CT can be recommended as a first-line modality for NPC restaging and monitoring.

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Impact of whole body PET CT in staging patients of carcinoma esophagus

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Aim: To assess the usefulness of PET CT in pretreatment evaluation of Ca Esophagus.

Introduction: Correct staging is critical as patients up to stage III are treated with surgery as well as chemotherapy and radiation treatment. Stage IV is non surgical and chemotherapy and radiotherapy are given as palliation. However complete resection of the primary tumour with lymphadenectomy are attempted when possible (as per National Cancer Institute, Esophageal cancer treatment summary dated 02-22-2006).

Materials: 44 recently diagnosed patients of Ca Esophagus post scopy and biopsy and CT thorax were included in the study.

Methods: All patients were subjected to Whole body PET CT scan performed 60 minutes after IV injection of 370 Mbq of F-18 FDG.The study was performed on a Whole body full ring dedicated PET-CT GE scanner(Discovery ST).The patients were divided into three groups based on the site of the lesion.

Group I: Lesion involving upper third esophagus (3 patients), Group II: Lesions involving mid third esophagus(17 patients) and Group III: Lesions involving lower third and GE junction (24 patients).

The PET CT findings were analysed in all the groups as follows:

Size and SUV of the lesion at the primary site.

Loco regional nodal involvement.

Distant metastases, including distant nodes or other distant metastases.

Size and SUV of the primary lesion and total number of FDG active lesions in each patient.

Analysis:
Group I- (3 patients): Loco regional nodes seen on CT in one patient showed no FDG uptake, hence the patient was down staged. Rest of the 2 patient had no change in stage as compared to pre PETCT stage.

Group II (17 patients): Four patients had distant metastases: Two patients had distant nodal metastases in supraclavicular nodes and two patients had other distant metastases(bones in one and bilateral adrenal in another) and thus were up staged.

Rest of the 13 patients showed no change in stage as compared to the pre PETCT stage.

Group III: In one patient the gastrohepatic node seen on CT showed no FDG uptake and in another patient the loco regional node seen on CT had no FDG uptake thus down staging the two patients.

Two patients had distant metastases:one patient had distant nodal (retroperitoneal-pre aortic node) and liver metastases and another patient had gastrohepatic nodes.

Rest of the 20 patients had no change in stage as compared to the pre PET CT staging.

Results: PET CT was able to change the staging in one out of 3 (33.3%)patients of upper third group, 4 out of 13 (30.7%)in the mid third group and in 4 out of 24 patients(16.6%) in the lower third and GEJ group.

Thus in 9 out of 44 patients (20.6%)PET CT changed the stage. Out of these 9 patients 5 patients were upstaged as M1 resulting in change in management of these 5 patients.

In rest of the 39 patients there was no change in management and PET CT improved the confidence level to go ahead with a curative treatment plan.

Size and SUV of the primary lesion and total number of FDG active sites were noted in each patient as important prognostic parameters to be compared with the post treatment follow up scan.

Discussion: PET is superior to CT and EUS combined in diagnosing Stage IV disease(Any T,Any N, M1)as shown in a study by Flamen et al quoted in Joint Programme in Nuclear Medicine December 9, 2003.

Further combined PET CT images have high sensitivity and accuracy in detection of lymph node metastases (Bar Shalom, et al., EJNM, Vol 32, No 8; August 2005).

Conclusion: In 9 out of 44 patients (20.6%)PET CT changed the stage.

Out of these 9 patients; 5 patients were upstaged as M1 resulting in change in management of these 5 patients.

Out of the remaining four patients, One patient in Group I and two patients of group II were down staged based on loco regional nodal status with no change in their curative treatment plan.

One patient in group III with gastro hepatic node involvement was treated with surgery and lymphadenectomy.

Thus in 39 patients(79.4%) there was no change in management and PET CT improved the confidence level to go ahead with a curative treatment plan.

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PRESENTATIONS & PANEL DISCUSSION:

CHALLENGES IN SETTING UP A PET PROGRAMME

DEVELOPING COUNTRIES - EXPERIENCE

Challenges in setting up a PET programme: Thailand experience

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The Current Status: The National Cyclotron and PET scan Center was established in Bangkok at Chulabhorn Cancer Center, Chulabhorn Research Institute (CRI) in May 2006. Under the vision of Professor Doctor HRH Princess Chulabhorn, the Founder and the President of CRI, the Center not only serves as an affilated diagnostic facility to the bench-to-bed researches at Chulabhorn Cancer Center, but a collabolative center among hospitals for this high cost technology. Three Medical schools namely Siriraj, Chulalongkorn, Ramathibodi and the National Cancer Institute have joined CRI in establishing the national PET programme from the beginning. HRH has dedicated Her efforts in planning, supporting, construction monitoring, equipment settling and connecting with international agency, mainly the IAEA, by Herself.

HRH's wish of the Center is to enhance utilazation of cyclotron and PET scan in the most cost effective way by sharing resources without discrimination. The concept has been appreciated by OAEP and IAEA as a model for developing countries. Until now, IAEA has contributed 5 fellowship training funds, 5 expert missions, 2 workshops, and 2 equipment setting procedures to the Center. It has served as an eduation and training module in basic and advanced PET techniques for Thai technicians, radiopharmacists, medical personnel, students and public on many occasions. A national congress on PET applications was held at CRI in August 2006 having 2 world renounced PET experts as invited lecturers. Conferences have been regularly arranged for Thai radiologists to exchange their experiences in PET interpretation.

From May 2006 to February 2007, FDG from the National Cyclotron and PET scan Center has been distributed 5 day a week to 4 PET services including 3 nearby university hospitals. At this 10-month period, 280 FDG-PET scans have been performed in patients from 31 hospitals. The services covered patients from urban and rural private hospitals (14 in Bangkok, 1 in a Northeastern province), university hospitals (7 in Bangkok, 1 in the North) and goverment hospitals (3 in Bangkok, 4 in rural areas, from north to south) including 1 from Pakistan. The services also included people from different levels of socioeconomical status. Most PET services were done in cancer patients. Among the most common applications were lung cancer, breast cancer, non-Hodgkin lymphoma, colon and nasopharyngeal cancers. FDG-PET were done in 9 epilepsy patients for presurgical evaluation. Two scans were done in patients with myocardial infarction.

The advantages of setting the National Cyclotorn and PET scan Center can be summarized as saving national bugdet from establishing several cyclotrons and scanners, sharing FDG among many PET centers, serving patients from different hospital settings, sharing experiences among experts, serving as education and training core center, performing multicenter clinical and basic researches, creating collabolative environment among institutes and serving as a model for future development.

The Future Challenges: The most challenging view of setting up a PET programme in a developing country is how to do it in the most cost effective way. Expansion of PET needs will challenge the way of setting up additional cyclotrons and PET scanners. With the half life of 110 minutes, FDG has limited time for delivery (less than 1 hour). The distance of FDG supply is therefore limited on ground transportation. The use of radiopharmaceuticals with shorter half lives will need scanner on the site of cyclotron and will affect location and distribution of the instruments. It is obvious that more cyclotron centers are necessary in the near future. They should be in equal distribution throughout the country. The facilities should be raised under appropriate timing and requirement. Experiences gaining from

the pioneer national center may help in cost effective settlement of additional centers in Thailand as well as in other developing countries.

Private hospitals or diagnostic practices can infleuce the concept of sharing resources as can alter the PET indications. This problem can probably be overcome by government reenforcement under health insurance policy for compensation.

The accelerated need of PET may cause inadequate supply of personnel. Education and training at the Center may partially solve the problem while abroad training for advanced knowledge is still necessary. Rapid changing PET techniques and growing new radiopharmacueticals are other challenging issues for developing countries.

Strategies in setting up a PET programme in developing countries are suggested: cyclotron and PET scan should be developed after or in parallel with corresponding modern medical facilities e.g. multidisciplinary cancer center or standard epilepsy surgery program. Collaboration among institutes are necessary. Additional PET centers and novel radiopharmacueticals should be developed step by step according to demand under proper timing. Cyclotrons should be regionally located while scanners should be equally distributed. For cost benefit practices, PET scan should be applied under evidence based indications or relevant research protocols. Thai Government as well as private sectors should follow HM the King's footsteps of sharing resources for sustainable development under self sufficient economy.

Challenges in setting up a positron emission tomography programme: Experience from Malaysia

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The nuclear Medicine Service in Malaysia started as a small unit in Kuala Lumpur, the capital city of Malaysia in 1964 as a unit under the Department of Radiotherapy. The expansion of nuclear medicine has been relatively slow from 1964 until 1990 with the existence of 3 units ie two in the Ministry of Health and one in the Ministry of Education.

It was in the 1990s onward that the expansion of nuclear medicine grew with the addition of 12 centres and in 2007 Malaysia has a total of 15 operational nuclear medicine centres operating with different capabilities.

The Ministry of Health, Malaysia authorized the installation of one medium energy cyclotron and two Positron Emission Tomography - CT Scanner in 2005 and the first PET-CT scanner went into operation in September 2005.

This presentation will give an insight of the triumphs and tribulations of setting the PET services in Malaysia: one centre with a Cyclotron on site and the other centre without a cyclotron and situated 370km away from the nearest cyclotron.

Some of the issues that had to be addressed to ensure smooth implementation of the PET-CT services are:

Before starting the service:

Attempts and efforts by the officers of various sections of the Ministry of Health in dealing with the justification and convincing the decision makers as to the need to have the service

- Justification for implementation of the Cyclotron, PET-CT services
- Selection of the Equipment/System
- Involvement of various authorities

During Implementation of the Service:

This section shall embark on the hiccups faced by the nuclear medicine fraternity in tackling the issue of where PET-CT should be placed and which authority shall be responsible for the cyclotron.

Issue of acceptance and over demand of the request for PET-CT examination and how to overcome the issues are touched upon in this section.

- Issue of whose turf: Radiology, Nuclear Medicine, Radiotherapy?
- Dealing with the Referring doctors
- Educating the hospital personnel
- Transportation of the radioisotope

- Trouble shooting events during scanning day

Evaluation of the service 1 year after starting the service

The service started with doing one day in a week for 3 months, followed by 2 days in a week for the next 3 months and then 3 days in a week for the next 6 months before embarking on a planned daily service. This section shall focus on the issues that are encountered and how we coped with the situations

- Dealing with patient comments
- Dealing with collegues expectations
- Ways of maintaining of standard of service.
- Dealing with problematic issues

Challenges and setting up a PET programme in Chile

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PET technology represents a big jump in the field of Nuclear Medicine, especially in oncology. There are several publications demonstrating that PET is a cost/effective and extremely valuable tool in diagnosis, staging, re-staging, treatment selection, evaluation and follow-up of patients suffering from cancer. In Chile, like in others developing countries, cancer is a serious health problem and a leading cause of mortality. Although this technique has been successfully introduced in most of the developed countries, in regions like Latin-America we still have difficulties incorporating this modality. However, our great challenge as specialist in Nuclear Medicine is to demonstrate that access to PET technology is widely justified. There are many questions to be answered before to establish a PET programme.

Where to install? Nowadays the main application of PET is in cancer patients, so the ideal location for this equipment should be a high level institution dealing with this disease as the first option. In our case the choice was FALP Oncology Clinic with 60 beds dedicated exclusively to fight again cancer in an integral way.

Which technology? From the technical point of view there are two main factors to bear in mind in equipment selection. These are: PET alone versus multimodality PET/CT. Due to enormous advantages of the last device, combining high CT anatomical resolution with PET metabolic information, the maximum effort should be done to introduce the hybrid modality. A second technological aspect deals with the crystal material and electronic of the PET's detector. Physical characteristics of GSO and LSO have some advantages over de BGO crystals.

Cyclotron: A critical point to set up a PET programme is to assure availability of positron emitting radiopharmaceuticals, namely ^{18}FDG. One alternative is to add a mini-cyclotron to the PET facility or utilize a local site as radiopharmaceutical provider. The first choice has considerable difficulties for a small center including financing, know-how, professional expertise, maintenance and QC. In our case we were lucky enough to count with the strong collaboration of the Chilean Nuclear Energy Commission and the visionary approach of its executives to install a medium size cyclotron able to produce large amounts of ^{18}F and other positron emitter like ^{11}C and ^{13}N.

Business Plans: PET or PET/CT settle requires a very precise business plan considering in-come and out-come. The main points to be evaluated are patient load, ^{18}FDG cost, other supplies, training, educational material, promotion, financial cost, depreciation, physical installation, taxes and other. Professional assistance in these matters is strongly recommended.

How to finance: Either in a private or public scenario the most probable situation is that financial support should be required. For a successful operation you must convince the financing authority that your programme is viable, your business plan shows profit and your down payment is acceptable. For some of these items vendor's help is extremely important.

Private or Public? Most of Latin-American countries had health systems based mainly in a socialized model. However, during the last decades striking economy changes have occurred in most of them. In Chile, one third of the population is under a private system. Since the public health budget is always insufficient, it is not easy to obtain priority from the government for advanced technology. To confirm this, according to our knowledge there are 31 PET systems in Latin-America, 28 of them installed in private institutions.

Personal requirements and training: Since PET/CT is a dual multimodality technique integration of both Nuclear Medicine and CT professionals is ideal. In our case combining these two areas was not a serious difficulty. According to our experience nuclear medicine technicians learned very quickly how to operate a CT with more expertise in radiopharmaceutical and radiation protection management.

Who reads the studies? Considering that this is a "fusion" technique all the studies should be read by qualified nuclear medicine physicians and radiologists simultaneously delivering a PET/CT "fusion" report.

Reimbursement: This is an extremely important aspect setting up a PET programme. Lack of reimbursement for PET or PET/CT studies is a serious limitation to sustain any business plan. This is an expensive technique for individuals and without health system coverage patient's access to this valuable technique should be significantly restricted. Any effort to obtain reimbursement codes must be done in advance. All the institutions involved should be mobilized to convince health providers that this is a cost/effective technique that finally will be of benefit both for the medical health system and for the patients.

In our particular case organizing the 8th WFNMB Congress in Chile in 2002 undoubtedly opened the door wide to a PET/CT Programme and certainly the installation of a cyclotron by the Chilean Nuclear Energy Commission was the key to access to this technology.

Challenges in setting up a PET programme – South African experience

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Positron emission tomography has over the last two decades been established as an important modality in Nuclear Medicine, especially in the management of oncology patients. In most parts of the developed world it is accepted as an integral part of the standard of care for many patients. The growth was even faster since the introduction of PET-CT devices.

In the developing world the expansion of PET facilities has been considerably slower, and in some regions no PET facilities are available. Numerous factors may be responsible for this phenomenon. As in the developed world, health care contraction and reform is also imminent in South Africa.

There are numerous constraints to the development of PET in South Africa. In contrast to the developed world, it took very long to establish PET facilities in South Africa, with the first facilities only established in late 2005, primarily in the private sector. Presently there are five private PET-CT facilities, with more expected in the near future. In the public sector the development is much slower. One PET-CT camera has been delivered, but is not yet functional, while two more will be installed soon.

Financial constraints in developing countries are seen as the most important obstacle in the development of PET. The need for basic services, such as clean water and sanitation also influences the decision. As South Africa has limited financial resources, careful attention has to be paid to the distribution of the health budget. One of the advantages South Africa has, is the availability of cyclotrons both in the north and the south of the country. This may assist with a more cost-effective approach, as each institution does not have to invest in the installation of a cyclotron. Work published by Keppler and Conti [1] confirmed that a PET-camera using external sources of radiopharmaceuticals was financially the most viable option. This, however, limits the radiopharmaceuticals to those labelled with F-18. Chuck et al also indicated that the per service cost for operating a PET facility in a regulatory environment is directly influenced by the number of studies performed [2].

The perception that a PET service is a tertiary or even quarternary service leads to opposition to its acquisition, with both clinical colleagues and decision makers questioning its application in South Africa. South Africa has a specific health policy, with the national Department of Health being responsible for tertiary and quarternary services, and the provincial governments for secondary services. The academic hospitals, where PET should be established, is therefore in a difficult situation, with funding allocated from the national department, but administrated by the provincial government. If the necessary funding for a PET service is not provided, it will be very difficult for the provincial government to fund it, more-so that the priority of the provincial administrators is on primary health care.

A problem that is more difficult to address, is the ignorance of decision makers about the value of PET. The absence of evidence based medicine on the use of PET in developing countries, especially regarding the unique disease profile of these countries, intensifies this problem. There is also an inherent distrust in the evidence provided by the developed world, which makes acceptance by decision makers in the health sector and in medical schemes difficult. Although there is evidence that

PET studies are cost-effective in certain clinical conditions, more evidence is needed to use this as a convincing tool. Especially that there are issues relating to the introduction of a new technology in a country with radically different incidences of pathology, in particular when there is a high background prevalence of HIV/AIDS as there is in South Africa.

Currently there is a shortage of staff with specific PET training, e.g. nuclear physicians, radiographers (technologists) and radiopharmacists and –chemists. Training institutions are looking into offering short courses for all the groups, while incorporating it into the existing curricula may take some time. There is also a lack of human resource capacity to train referring clinicians about the value of the technique in a clinical practice.

PET imaging is developing rapidly elsewhere in the world. Hence health technology reviews performed one or two years ago are lagging behind. The time is ripe for a breakthrough with providing an organised national service for PET, also in South Africa. This technology development should be regarded as a necessity, and part of strategic planning of the National Department of Health. Numerous aspects of the recommendations of the Intercollegiate Standing Committee on Nuclear Medicine in the UK are also applicable in South Africa and can be used by all role players in the field [3].

It is already clear from the current private practices that implementation of the technique is heavily influenced by reimbursement restrictions. These should also be addressed in collaboration with the health funders in South Africa, to ensure the viability of PET in the public and private sector.

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Economics of PET service

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PET ONCOLOGY III

Emerging clinical PET tracers for oncology (FLT, Choline, Acetate)

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^{18}F-FDG PET has been shown to be helpful for the diagnosis of primary, recurrent, and metastatic lesions in a variety of tumors. However, problems exist in the diagnosis of tumors with low metabolism, such as prostate tumors, low-grade sarcomas, low-grade lymphomas, and well-differentiated hepatocellular carcinomas. ^{18}F-FDG PET for the diagnosis of primary prostate cancer is not highly effective, at least for wide clinical use. Over the past years, novel PET tracers have been introduced that may potentially balance the encountered weak points in cancer detection and staging with ^{18}F-FDG PET. Apart from ^{11}C- and ^{18}F-choline, ^{11}C-acetate (AC) seems to be highly promising in a variety of tumor types [1]. Shreve et al [2] and Shreve and Gross [3] were the first to report on the high uptake of AC in renal cell carcinoma and the tracer's potential to clearly differentiate between malignant and benign tissues. In the meantime, various working groups have tested the potential of AC PET imaging in prostate cancer diagnosis [4-10] and provided encouraging results. AC showed a marked uptake in prostate cancer and was clearly more sensitive in detecting prostate cancer than ^{18}F-FDG PET. Due to the mostly low FDG uptake in prostate cancer, other radiopharmaceuticals have been studied: ^{11}C-choline and ^{18}F-labeled choline derivatives, including ^{18}F-fluoroethycholine and ^{18}F-fluoromethylcholine (FCH). High physiological uptake of choline and fluorinated derivatives in the liver, pancreas, bowel, and urinary excretion system [10,11] may limit clinical utility of these radiotracers. In prostate cancer Hara and coworkers [11,12] compared ^{11}C-choline with ^{18}F-labeled choline and found, in terms of spatial resolution, FCH has a slightly higher image quality than the 11C-labeled tracer; contrary to ^{11}C-choline, FCH is eliminated via the kidneys. With FCH PET, performing dynamic acquisition (starting 1 min pi) is helpful [13,14] to differentiate focal ureter activity versus pathological lymph nodes in the pelvis: focal FCH uptake from the very beginning (minutes 1-4) has to be interpreted as malignant (lymph nodes and bone), while that occurring in later frames (minutes 5-8) as tracer in the ureter. FCH in the urinary bladder also appears at approximately 5 to 8 min pi. [13,14]. Both, ^{18}F-choline and ^{11}C-acetate PET/CT studies succeeded in detecting local residual or recurrent disease in about half the patients with PSA levels of <1 ng/mL after RP [15], these studies cannot yet be recommended as a standard diagnostic tool for early relapse or suspicion of subclinical minimally persistent disease after surgery. Endorectal MRI might be more helpful, especially in patients with a low likelihood of distant metastases. Nevertheless, further research with ^{18}F-choline and ^{11}C-acetate PET/CT with optimal spatial resolution might be needed for patients with a high risk of distant relapse after RP even at low PSA values. Also, PET with ^{11}C-choline and ^{18}F-fluorocholine has demonstrated efficacy for detection of gliomas, which was validated by image-guided stereotactic biopsy [16].

^{18}F-FLT is now being evaluated at a number of PET centers worldwide as the radiotracer for imaging tumor proliferative activity. FLT is an analogue of thymidine and is phosphorylated by cellular thymidine kinase dyring the S-phase of the cell cycle to it's monophosphate form and metabolically entrapped inside the proliferating tumor cell. It can be used to readily image a number of different tumor types, e.g., as lung, breast, brain, and esophageal tumors. Initial PET imaging studies with ^{18}F-FLT demonstrated that it can produce high-contrast images of tumor, such as lung cancer [17]. In addition, physiologic uptake is observed in the bone marrow, a highly proliferative organ, and in the liver, kidneys, and bladder as a result of glucuronidation and clearance. ^{18}F-FLT uptake has been found to generally correlate with proliferation of tumor, when compared to measurement of Ki-67 levels made on biopsy specimens [18,19], but this has not been found in all situations [20]. Overall, it appears to produce images with less contrast than ^{18}F-FDG, except in the brain [20-23]. Nevertheless, ^{18}F-FLT PET is most likely to find use in measuring treatment response via changes in tumor proliferative activity. The other pyrimidine that has been carefully evaluated is FMAU, which was

originally labeled by Dr. Conti and colleagues [24] with ^{11}C and subsequently labeled with ^{18}F by Dr. Mangner and colleagues [25,26]. FMAU has the potential advantage that, like thymidine, it is incorporated into DNA [24,27]. It resists degradation, but is rapidly taken up and trapped in the liver, probably associated with glucuronidation. Its rapid liver uptake appears to decrease clearance into the kidneys and bladder, allowing for improved imaging in the pelvis compared to FLT and FDG. As a result, FMAU can be used to image primary tumors within the prostate [28]. Less FMAU retention is seen in the bone marrow, compared with that found when imaging with labeled thymidine or FLT. This may be attributable to differences in transport of the tracers, but further study is required to understand these differences and assess the impact on imaging of various tumor types. In any case, lack of marrow uptake does have the advantage in that bone metastases can be detected in patients with metastatic prostate cancer [29].

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Molecular imaging in quality health care

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Quality Health Care results from applying fundamental basic science and preclinical concepts as well as novel technologies to patient care within specific socio-economic frameworks. Cancer mortality has improved recently but outcomes of cancer patients are still unacceptably poor.

Molecular Imaging has the potential to improve the outcome of cancer patients in several ways. In the preclinical setting, high resolution molecular imaging devices designed for small animal research have developed into valuable tools for drug evaluation and imaging probe design. These have enabled us to study drug effects in vivo by monitoring longitudinally their effects on tumor cell metabolism or proliferation.

The success of Imatinib in treating chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GIST) has demonstrated that targeted drugs can induce remarkable tumor responses and may even cure cancer patients. Targeted drugs have been used for treating various common solid human tumors, including breast cancer, colorectal cancer, and non-small cell lung cancer. However, diverse signaling pathways are involved in the development and progression of these genetically heterogeneous diseases. Consequently, inhibition of one specific pathway is likely to be efficacious in only in small subsets of patients with specific histological tumor types.

It is unlikely that a single "blockbuster" drug can be effective for all patients with a “common” tumor. Rather, it will be necessary to develop multiple targeted drugs even for patients that share a single histologically defined tumor type. The inevitable consequence is a decreased revenue/cost ratio for the industry and increasing costs for patients and health care systems. It is therefore of paramount importance to identify drug failure as early as possible in preclinical and clinical trials.

Human studies with positron emission tomography (PET) with molecular imaging probes targeting physiological processes such as glycolysis, lipid synthesis, amino acid transport, cell surface receptors, gene expression and others are available for evaluating in animal experimental studies and humans the extent of disease as well as treatment effects in vivo.

With the advent of PET/CT anatomic and molecular images can be fused affording assignment of normal or abnormal molecular imaging findings to specific anatomical structures. The major vendors have invested millions of dollars into bringing together the highest quality CT with “state of the art” PET instrumentation. Similar technology mergers are currently happening for PET and MRI.

These technological advances come at a time of increasing health care expenditures worldwide. One must therefore carefully evaluate whether the increasing costs are met by increasing effectiveness of the technology. This needs to be carefully determined within the varying health care systems and frameworks.

This presentation will provide cancer statistics, introduce molecular imaging tools and will describe the concept of targeted imaging. Animal experimental studies will be used to demonstrate promising treatment approaches in vivo and how imaging can be used to monitor therapeutic effects. Further, the clinical molecular PET/CT imaging technology will be introduced and its impact on patient management and cost-effectiveness will be reviewed and discussed within the confines of different health care systems.

Finally, Initial clinical trials will be presented that use molecular PET rather than anatomical CT imaging for prospectively arriving at patient management decisions.

Receptor PET/CT with Ga-68 labeled somatostatin analogues for the diagnosis, staging and restaging of patients with neuroendocrine tumors undergoing peptide receptor radionuclide therapy – Current status and future perspectives

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Background: Neuroendocrine tumors (NET) are rare, heterogeneous in nature and they often show an indolent course. The clinical diagnosis of functional NET - based upon typical symptoms and biochemical markers - is relatively easy; however, a significant number of NET is non-functionally active and are diagnosed usually at a late stage.

The functional information provided by receptor PET/CT (using positron emitter labelled somatostatin receptor analogues) along with the possibility to obtain semi quantitative or even fully quantitative data, has resulted in the conceptualization of a 'tailored therapeutic regime' following the concept of personalized medicine. PET/CT, apart from providing functional information about the whole body, makes it possible to perform a diagnostic CT scan at the same time - whenever needed – thus giving essential information regarding the size, number and exact localization of the lesions, keeping in mind that not all the tumors/metastases might be sstr positive.

The development of generators for the production of positron emitters is triggered by the high costs associated with the establishment and maintenance of a cyclotron. The ^{68}Ge/^{68}Ga-generator was already mentioned decades ago (Green and Tucker 1961), but its use was very limited until a new ^{68}Ge/^{68}Ga-generator system (Roesch et al. J Nucl Med 2007) became available in 2004. ^{68}Ga ($t_{1/2}$ =68 min) is a positron emitter with excellent properties (89% positron emission). The long half life of the mother radionuclide ^{68}Ge (270.8 days) enables use of the generator for nearly 9 months (up to 1 year depending upon the demand of a particular center).

The short half life (68 minutes) of Ga-68, its ideal chemistry for labeling and above all, its inexpensive, generator-based production (less than 20 € per patient dose depending on the number of studies per year) has resulted in wide success of Ga-68 labeled somatostatin analogues in the management of patients with NET. Although there are various somatostatin analogues available, DOTA-NOC and DOTA-TOC (and less frequently DOTA-TATE) are most widely used. DOTA-NOC has higher affinity to sstr 3 and 5 making it possible to detect a wider spectrum of SSTR positive NET.

Prior to performing Ga-68 DOTA-NOC PET/CT, patients should be withdrawn from 'cold' octreotide therapy in order to prevent competitive inhibition of Ga-68 DOTA-NOC uptake by NET. Sandostatin LAR injections should be stopped 4 weeks prior to the scan and s.c. treatment with octreotide should be paused at least 2 days before. Care is taken for proper hydration of the patient. Prior to the acquisition 1.5 L of water-equivalent oral contrast dispersion e.g. gastrografin, is given.

Clinical Indications: If there is strong suspicion of a GEP tumor, or if a NET has been proven by immunohistochemistry, receptor PET/CT (or SMS scintigraphy) should be the <u>first</u> diagnostic procedure for staging (even before CT and MRI) as well as for planning peptide receptor radionuclide therapy (Y-90 DOTA-TATE or Lu-177 DOTA-TATE). Further indications are follow-up after surgery and the diagnosis of recurrences in case of increasing tumor markers; the evaluation of therapy response after PRRT, chemotherapy or biological therapy; and the differential diagnosis of neuroendocrine tumor vs. non-endocrine tumor in case of a space occupying mass, if a final diagnosis can not be obtained by biopsy or operation.

Conclusions: During the last 3 years, more than 2,000 receptor PET/CT studies using different Ga-68 labeled DOTA-SMS-analogues were performed in our center. The results clearly demonstrate that there is an essential role for receptor PET/CT in the pre therapeutic evaluation (determination of receptor density) and in the follow-up after treatment with radio labeled peptides. Receptor PET/CT using Ga-68-labelled DOTA-NOC or other SMS analogues enables the molecular imaging of neuroendocrine tumors with very high diagnostic accuracy and is becoming the gold standard for imaging of neuroendocrine tumors.

Future Perspectives: Longer lived positron emitters (e.g. Cu-64 or Sc-44) could enable an accurate patient-specific pre-therapeutic dosimetry before peptide receptor radionuclide therapy (individualized therapy). Apart from somatostatin analogues, there are several other PET radiopharmaceuticals which are currently under investigation for the diagnosis of NET and other tumors expressing G-protein coupled receptors.

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The value of the PET/CT FDG in the diagnostics of ovarian cancer in patients with an increased level of Ca 125 marker

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Ovarian cancer almost always grows in insidious ways and is diagnosed at a stage that does not enable effective treatment. In patients with this kind of neoplasm, PET with [F-18] fluorodeoxyglucose (FDG) is more sensitive and specific than CT, MR. The Ca 125 level is used for monitoring the cancer but without anatomical localization of the lesions. The aim of this study was the retrospective assessment of the value of the PET/CT in the diagnostics of the group of patients with an increased Ca125 level.

Material Methods: In the time between March 2003 and October 2006, 326 studies were performed to diagnose recurrent ovarian cancer. We selected 68 women (age 55,1±10,2) where the reason for conducting the PET/CT study was an increased level of Ca 125 without any signs of the disease using other imagining techniques. PET/CT studies were made on the Siemens Biograf LSO scanner according to typical PET protocol. Patients were divided into 3 groups according to their PET/CT results: absence of lesions(7 patients), presence of singular lesion (14 patients), presence of multiple lesions (47 patients). We assessed the Ca 125 level and SUV max. in these groups.

Results: In the group without pathological lesions in PET/CT, Ca 125 level and SUV max. were 136,8±110,7 and 17,8U/ml respectively, with one cancer lesion Ca 125 was 193,1±221,4 U/ml and SUV max. was 13,9±12,6, with multiple lesions the Ca 125 level and SUV max. were 487,8±661,3 U/ml and 10,7±4,6 respectively.

Conclusions: 1. Probability of finding changes in PET/CT, in the case of patients with pathological level of CA 125, rises with an increase in the cancer's marker level.

2. The values of the lesion's SUV is not dependent on the marker's level.

3. There is a need to define the Ca125 level's border which below performing the PET/CT study in a group of patients with ovarian cancer is not effective.

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PET/CT imaging in multiple myeloma; Ankara University experience - Preliminary results

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Aim/Background: Multiple myeloma (MM), malignant B cell and plasma cell disorder, involves the skeleton in more than 60% at diagnosis. Conventional and radionuclide methods are routinely used to evaluate these lesions. Recently, FDG PET/CT has been introduced to the field. In this study, our aim was evaluate the accuracy of FDG PET in detecting myeloma lesions and its influence on patient's management comparing with clinical, radiological and bone scintigraphic findings.

Methods and Materials: 34 patients (10 female, 24 male) were evaluated; group I had 26 patients (8 female, 18 male; aged 32-83 years) with multiple myeloma, group II had 4 patients (1 female, 3 male; aged 35-72 years) with solitary plasmocytoma and group III had 4 patients (1 female, 3 male; aged 37-60 years) with monoclonal gammopathy. Mean follow up period was 18,1±17,6 months. In group I; 2 patients were referred for evaluation of extent of disease before bone marrow transplantation (BMT) and 1 patient was referred for assesment of BMT response, 7 patients had pain and were referred for assesment of the extent of disease, and other patients with no complaints were in follow up. In group 2 and 3, PET/CT was performed to evaluate the extention of disease. The results of whole body bone scintigraphy (WBS), radiographs, and MRI or CT imaging modalities as well as the clinical course at the same period were used to compare with FDG PET/CT results (Table 1).

TABLE 1. COMPARISON OF PET RESULTS WITH RADIOLOGICAL EXAMINATIONS

	Group I n:26		Group II n:4		Group III n: 4	
Radiologic exam	PET (+) n:16	PET (-) n:10	PET (+) n:1	PET (-) n:3	PET (+) n:3	PET (-) n:1
(+)	13	2	1	-	3	-
(-)	3	8	-	3	-	1

Discussions: PET/CT scan is helpful to evaluate MM patients. It appears to be more sensitive than other radiologic and scintigraphic examination for the detection of lytic bone lesions. However, it may not be sufficient for detection and differentiation of small lesions and diffuse marrow involvement. In this study, 2/34 patients had negative PET/CT and positive bone lesions. It was thought that the combination of PET/CT and other radiological and scintigraphical examination might be more succesfull than PET alone. Since PET investigation was performed mostly during active disease evaluation of its impact on survival, response was not avalaible. It is also important to emphasize the disadvantages of PET/CT in myeloma treatment, steroid related hyperglycemia, early vertebrate operations the frequently performed cause false positivity. However, we took precautions to delay imaging untill 3 months following surgery and avoding imaging during glucose intolerance.

Conclusions: PET/CT has the applicability to whole body imaging which is hard to apply to MRI and results with better resolution compared to whole body MRI.

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RADIOPHARMACY

A new generation of radiometal-based radiopharmaceuticals for PET oncological imaging

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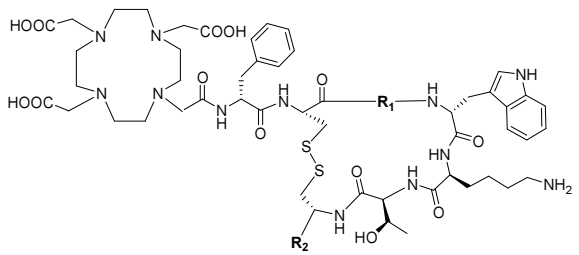
Positron emission tomography (PET) is established for the diagnosis and management of cancer in both research and clinical settings. The diverse nature of cancer will require a multitude of PET radiopharmaceuticals to target the many types of receptors and enzymes that are overexpressed in tumors. There are many exciting new agents that are at either the preclinical evaluation or clinical trial stage. This synopsis will focus on a few of the radiometal-based agents labeled with ^{68}Ga ($T_{1/2}$ = 68 min; β^+ (88%; 1.88 MeV)) and ^{64}Cu ($T_{1/2}$ = 12.7 h; β^+ (17.8%; 0.655 MeV)) that show promise for PET imaging of tumor receptors.

Gallium-68 is produced from the ^{68}Ge/^{68}Ga generator. The long half-life of the parent nuclide ^{68}Ge ($T_{1/2}$ = 270.8 days) allows the generator to be used for 1-2 years, making ^{68}Ga radiopharmaceuticals relatively economical compared to cyclotron-produced PET radionuclides. This generator is now commercially available, providing further motivation for the development of new ^{68}Ga radiopharmaceuticals. Gallium-68 has been most widely labeled to ligands binding to somatostatin receptors, and these agents have been evaluated both in tumor-bearing rodent models and humans. Maecke *et al.* have compared somatostatin analogs (Figure 1) labeled with gallium radionuclides for their internalization into tumor cells and uptake in somatostatin receptor-positive tumors in various rodent models (for a recent overview, see [1]). These studies showed ^{67}Ga-DOTA-NOC had the most optimal tumor:blood ratios in tumor-bearing mice, although ^{67}Ga-DOTA-TOC demonstrated lower liver uptake. The Bad Berka group in Germany has more than 2 years' experience employing ^{68}Ga-labeled somatostatin analogs in somatostatin receptor-positive tumor patients, mainly those with gastroenteropancreatic (GEP) tumors [2]. A direct comparison was performed in patients with neuroendocrine pancreatic tumors demonstrated superior image quality with ^{68}Ga-DOTA-NOC compared to ^{68}Ga-DOTA-TATE, with SUVs as high as 150 for ^{68}Ga-DOTA-NOC [1]. The ease of synthesis and availability of ^{68}Ga-labeled agents will make this class of radiopharmaceuticals highly desirable for PET centers throughout the world.



Compound	R_1	R_2
DOTA-TOC	Tyr	Thr(ol)
DOTA-TATE	Tyr	Thr
DOTA-NOC	Nal-1	Thr(ol)

Figure 1: Structure of DOTA-somatostatin analogs

Copper-64 can be effectively produced by both reactor-based and accelerator-based methods. The most widely used method for the production of no-carrier-added ^{64}Cu is *via* the ^{64}Ni(p,n)^{64}Cu reaction on a biomedical cyclotron as proposed by Szelecsenyi *et al.* [3] has been scaled up for production of large amounts (up to 37 GBq (1 Ci)) of ^{64}Cu for diagnostic imaging and cancer therapy applications [4]. The 12.7 h half-life of ^{64}Cu and the ease of producing large quantities at relatively low cost (~$10/mCi in the U.S.) allows overnight shipment, making this radionuclide attractive for clinical studies. One of the challenges of developing ^{64}Cu radiopharmaceuticals is having chelators that stably complex ^{64}Cu(II), as Cu(II) is a very labile metal ion, and will readily bind to many proteins *in vivo*. Typical chelators used to attach ^{64}Cu to biomolecules for imaging applications include macrocyclic chelators such as DOTA and TETA. Sun *et al.* introduced a cross-bridged macrocycle (CB-TE2A; Figure 2) that forms a highly stable complex with Cu(II) *in vivo* [5]. Three different receptor-targeting peptide systems have been conjugated with CB-TE2A for imaging with ^{64}Cu [6-8].

The $\alpha_v\beta_3$ integrin is a widely-studied receptor system that facilitates imaging of tumor angiogenesis. Chen *et al.* presented biodistribution and microPET imaging results on monomeric, dimeric and tetrameric ^{64}Cu-DOTA-conjugated RGD peptides [9,10]. In the MDA-MB-435 human breast cancer tumor-bearing mouse model, the dimeric agent showed tumor uptake of 3-4% ID/g, and at 2 h post-injection the tumor:blood ratio was approximately 20. The tumor:muscle ratios were relatively low (~10), however. The tetrameric ^{64}Cu-labeled RGD peptide was recently investigated in a UG87MG glioma tumor-bearing mouse model and this tracer showed improved tumor:blood and tumor:muscle ratios of 35 and 16, respectively. A CB-TE2A-RGD analog was recently reported for imaging increased numbers of osteoclasts in a model of pharmacologically induced osteolysis [6]. This agent had improved pharmacological properties compared to the DOTA-RGD analog.

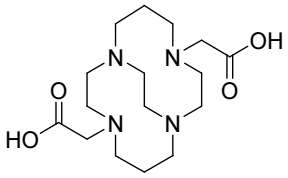


Figure 2: CB-TE2A

In summary, there are radiometal-labeled PET radiopharmaceuticals that show promise for clinical use in cancer imaging. This synopsis highlights ^{68}Ga- and ^{64}Cu-labeled agents that exhibit great potential for imaging somatostatin receptors and the $\alpha_v\beta_3$ integrin.

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Chemistry of potent tracers for PET studies of neuronal functions

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While the major domain of oncological PET imaging concerns diagnosis, PET-studies of neuronal functions additionally comprise to a greater extent basic research of normal and disturbed molecular processes in physiology as well as pharmacology; this also in drug development and evaluation. The tracers used for these purposes are mainly low molecular, often neutral and rather lipophilic compounds, which is especially true for ligands of the CNS in order to cross the BBB, and thus are covalently labelled with non-metallic radionuclides.

Carbon-11 ($T_{1/2}$ = 20.4 min) and fluorine-18 ($T_{1/2}$ = 109.7 min) are clearly the most suitable radionuclides and are predominantly used in PET imaging, each with special advantages. However, some non-standard positron emitters are gaining interest in order to meet special pharmacological and/or kinetic requirements with respect to tracers' metabolism (stability), (slow) biodistribution, shape, lipophilicity etc. Worth mentioning are isotopes of the higher halogen homologues bromine-76 ($T_{1/2}$ = 16.0 h), iodine-120 ($T_{1/2}$ = 1.35 h) and iodine-124 ($T_{1/2}$ = 4.15 d) as well as the sulphur-analog selenium-73 ($T_{1/2}$ = 7.1 h), which allow to expand the versatility of tracers and concepts of studies.

Labelling methods applicable with these nuclides naturally depend on and are as different as their elements' chemical nature. The fast and reliable preparation of standadized, short lived products for clinical and experimental use must meet the requirement of a high molar activity of generally ≥ 100 GBq/μmol. Although mandatory for receptor- and transporter-ligands, enzyme substrates and generally for tracers with high pharmacological or toxicological potency, a high molar activity is generally recommended in order to lower the chemical burden during synthesis, isolation and administration of radiotracers.

A series of tracers is available for measurements of basic functions of (neuronal) tissue such as $[^{15}O]O_2$ for oxygen extraction, $[^{15}O]H_2O$ and $[^{15}N]NH_3$ for perfusion in brain and heart, respectively, $[^{11}C]CO$ for blood volume and [^{18}F]FDG for the energetic turnover. Furtheron, many clinically established radiopharmaceuticals, mainly receptor ligands [1], for diagnosis and research may be mentioned for heart: [^{11}C]hydroxyeplidrine, [^{11}C]acetate, [^{11}C]GCP12177 and brain: [^{11}C]raclopride, [^{11}C]flumazenil, [^{18}F]FDOPA, [^{18}F]altanserine, [^{18}F]setoperone, [^{18}F]metylbenperidol etc., while a bigger variety is under clinical evaluation: [^{11}C]PK11195, [^{11}C]6-OH-BTA-1 ([^{11}C]PIB), [^{18}F]A-85380 [^{18}F]fluroethyl-flumazenil, [^{18}F]cyclofoxy, [^{18}F]MPPF, [^{18}F]fallypride etc.
A still bigger group represents the radiotracers under investigation with potential use in neuronal PET studies. A few need to be mentioned, e.g. [^{11}C]SCH23390, [^{11}C]FLB457, [^{11}C]WAY100635, 4-[^{18}F]fluorometaraminol, [^{18}F]FDDNP, besides the many ligands based on the cocaine- or diphenylsulphide-structures with specificity for the dopamine transporter and serotonin reuptake transporter, respectively, e.g. [^{11}C]MADAM, [^{11}C]DASB, [^{18}F]AFB, [^{18}F]FP-CIT or [^{18}F]FE@CIT. Especially the last groups make clear the broad and elaborate radiosynthetic efforts necessary in order to develop optimally suited tracers. Although there are "standard" procedures available these must be specifically adapted almost for each new compound.

For carbon-11 and fluorine-18 from the many procedures developed over the last 30 years, only a few primary labelling agents, i.e. $[^{11}C]CO_2$, $[^{11}C]CO$ and [^{18}F]fluoride, have gained practical importance and were proven to be useful to meet those criteria. In fact, [^{18}F]fluoride is still the only species to achieve high molar activity products. More complex molecules deserve tedious multistep built-up reactions and n.c.a. [^{18}F]fluoroarenes of high electron density are still a challenge [2]. 6-[^{18}F]Fluoro-DOPA and 4-[^{18}F]fluoro-metaraminol can be mentioned here as examples, where complex

nucleophilic synthetic pathways still make c.a. electrophilic labeling advantageous or exclude the clinical use, respectively. Electrophilic radiofluorination generally relies on carrier-added generation of elemental $[^{18}F]F_2$, while a newer more complicated method using n.c.a. $[^{18}F]F^-$ and electrical discharging is not yet on the level of high molar activities.
In the case of carbon-11 [3,4], $[^{11}C]CO_2$ can directly be used to produce carboxylic acids and derivatives thereof and $[^{11}C]CO$ finds increasing application. However, the secondary labelling agent $[^{11}C]$methyl iodide and triflate are most widely applied. Here, the more classical "wet" method by reduction of CO_2 with $NaAlH_4$ in solution must be compared with the "dry" conversion of $[^{11}C]CH_4$ with I_2 in gaseous phase with respect to reliability of high molar activity production under practical conditions.

Thus, reliable production of standardized radiotracers, relies on relatively few principal methods which are adapted to the compound of interest, and making use of modern synthetic concepts and technical advances such as electrochemistry, microwave and micro fluidic systems/micro-reactors. Those radiochemical aspects will be exemplified and discussed with selected tracers mentioned above.

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The ^{68}Ge/Ga radionuclide generator: Processing and potential for radiopharmaceutical chemistry and nuclear medicine

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Radionuclide generator systems continue to play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine, oncology and interventional cardiology. Key advantages for the use of radionuclide generators include reasonable costs, the convenience of obtaining the desired daughter radionuclide on demand, and availability of the daughter radionuclide in high specific activity, no-carrier added form. Although many parent/daughter pairs have been evaluated as radionuclide generator systems, in particular for the application of labeled PET radiopharmaceuticals, there is a relatively small number of generators which are currently in routine clinical and research use. Recently, the ^{68}Ge/Ga and ^{72}Se/As systems have found impressive application, but also the ^{44}Ti/Sc generator represents a promising system.

The ^{68}Ge/Ga generator (^{68}Ge, T½ = 270.8 d) provides a cyclotron-independent source of positron-emitting ^{68}Ga (T½ = 68 min, β_{β}^{+} branching = 89%), which can be used for coordinative labelling. Recently, tumor imaging using ^{68}Ga-labelled DOTA-conjugated peptides became one of the most exciting approaches to diagnose neuroendocrine and other tumors and metastases because (i) octreotide derivatives with high affinity and selectivity to somatostatin receptor expressing tumour cells are available, (ii) syntheses of DOTA-conjugated targeting vectors are straight forward due to the kit-type labelling, and (iii) PET/CT scanners perfectly correlate morphological and functional parameters. However, for labelling of biomolecules via bifunctional chelators, ^{68}Ga(III) as eluted initially need to be pre-concentrated and purified from ^{68}Ge(IV), Zn(II), Ti(IV) and Fe(III).

We describe a system for simple and efficient handling of the ^{68}Ge/^{68}Ga generator eluates with a micro-chromatography column filled with about 50 mg of a cation exchange resin (Bio-Rad AG 50W-X8) as the main component. Chemical purification and volume concentration of ^{68}Ga are carried out in a 80% acetone/0.15 M HCl solution. Finally, more than 97% of ^{68}Ga are obtained in 400 µl of a 97.6% acetone/0.05 M HCl solution. The initial ^{68}Ge contamination of the eluate was reduced by a factor 1000. Contents of Zn(II), Fe(III) and Ti(IV) were reduced significantly. Consequently, the processed fraction can be used directly for the syntheses of radiopharmaceuticals. For labelling with ^{68}Ga(III), DOTA-octreotides (DOTATOC, DOTANOC) and Desferrioxamine-B-succinyl-octreotide (DFOOC) were used. Within 25 min, an injectable radiopharmaceutical, e. g. ^{68}Ga-DOTATOC can be prepared with specific activities of up to 450 MBq/nmol. The developed system represents a simple and efficient way for labelling of DOTA-conjugated biomolecules with generator-produced ^{68}Ga(III). [^{68}Ga]DOTATOC and [^{68}Ga]DOTANOC were successfully used in a series of human somatostatin receptor-expressing tumours diagnosis with PET/CT. Moreover, a variety of other ^{68}Ga labelled compounds might be synthesised for many other applications.

Despite of high-resolution PET imaging, the ^{68}Ge/Ga and ^{44}Ti/Sc generators might also be used in combination with therapeutic approaches. Both ^{68}Ga, but eventually even better ^{44}Sc might be labeled to chemically similar targeting vectors such as DTPA- or DOTA-conjugated peptides, antibodies or antibody fragments. This might allow for better pre-therapeutic diagnoses in terms of tumor detection and radiation dosimetry, prior to the application of analogue radiotherapeuticals labeled with ^{90}Y, ^{177}Lu or other particle emitting trivalent metals radionuclides.

Due to the long half-life and the low cross sections, in particular for the parent nuclides ^{68}Ge and ^{44}Ti, the production rates are relatively low and require long high-current irradiations. Although this results in rather high cost per generator, the number of PET scans achievable (up to several hundreds per single ^{68}Ge/Ga generator for example) definitely lowers the costs per individual patient investigation.

Finally, the ^{68}Ge/Ga and ^{44}Ti/Sc generators offer a kit-type synthesis of PET radiopharmaceuticals. This might become a significant advantage when compared to ^{11}C or ^{18}F labelled PET tracers, in particular in centres without a cyclotron and / or without a sophisticated organic synthesis infrastructure and experience. With new kit type compounds to be developed for coordinating generator derived ^{68}Ga or ^{44}Sc, there will be a fascinating perspective for several systems, which partly might introduce PET in directions, today (still) covered by similar ^{99}Mo/^{99m}Tc generator systems and SPECT.

In conclusion, the current level of radiochemical development and radiopharmaceutical investigation clearly indicates a significant potential of the ^{68}Ge/Ga generators, for applications both in basic research and for routine application in state-of-the-art nuclear medicine. In particular for countries or medical centres, not yet running medical cyclotrons and/or not yet owing sophisticated organic radiopharmaceutical production infrastructure, the availability of the ^{68}Ge/Ga generator might help to start PET chemistry developments and patient diagnoses using PET.

Synthesis of [^{18}F] Fluromisonidazole using a general purpose fluorination module and combination purification column

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Nitroimidazoles are a class of compounds that are selectively trapped in hypoxic but viable cells. [^{18}F] –Fluoromisonidazole ([^{18}F]-FMISO) is the most studied and used hypoxic agent of the several that have been described [1,2,3]. There are two different labeling approaches for [^{18}F] FMISO. The most promising direct labeling approach of [^{18}F]-FMISO seems to be nucleophilic substitution with $^{18}F^-$ of the tosylate–leaving group on the tetrahydropyranyl-protected precursor 1-(2´-nitro-1´-imidazole)-2-O-tetrahydropyranyl-3-O-toluenesulphonylpropanediol (NITTP) followed by acid hydrolysis of the protecting group [1].

In this abstract, we report the synthesis of [^{18}F]-FMISO using a general purpose fluorination module and an indigenously developed combination-column composed of anion exchanger and neutral alumina for purification. A reasonably shortened synthesis time and satisfactory yields were observed.

$^{18}F^-$ produced in the Cyclotron [^{18}O (p, n) ^{18}F] is trapped in a small anion exchange column (Chromafix 45-PS-HCO_3) and eluted into the reaction vessel in the form of TBA^{18}F (Tetrabutyl Ammonium Fluoride). Excess DNA-grade acetonitrile was added and the mixture distilled azeotropically until the TBA^{18}F was dry. To this is added NITTP, 25mg in 0.6 ml acetonitrile and heated to 110˚C for 15 minutes for the nuclephilic fluorination. The reaction mixture is brought to near-dryness with heat, vacuum under He-gas. 1ml HCl (1M) was then added to the dry reaction mixture and heated to 105˚C for 10 minutes to hydrolyze the tetrahydropyranyl protecting group.

The reaction mixture is cooled and passed through the purification column. The reaction mixture is rinsed with 1 ml 5% ethanolic water and passed through the column. Finally, [^{18}F]FMISO was eluted with 14 ml 5% ethanolic water in the product vial already having 1.7 ml 10% NaCl and 0.7 ml 1(M)NaH_2PO_4 to maintain acceptable pH and isotonicity of the product.

The final product is then dispensed through 0.2μ filter into sterile and bacterial endotoxin-free evacuated vials. QC analysis consists of confirming the radiochemical purity by TLC in 95:5 MeOH: NH_3, radionuclidic identity by $T_{½}$ measurements, checking the pH by pH paper and visual check of clarity. Sterility and bacterial endotoxin tests were done on samples post radioactive decay.

The quality of the [^{8}F]-FMISO synthesized is satisfactory from all respects. The final product is clear and colourless. The RCP of [^{18}F]-FMISO was >95% (R_f of 0.65 – 0.75 in MeOH: NH3 [95:5]) and this was confirmed by TLC of the reference standard (^{19}FMISO) and staining with iodine vapour (Fig. 1). Radiochemical stability of the product in saline (1 ml [^{18}F]-FMISO + 9 ml saline) was checked up to 6h by TLC. The radionuclidic identity was confirmed to be $^{18}F^-$ by $T_{½}$ measurements (110±5 minutes). All the batches produced passed the sterility and bacterial endotoxin tests. The total synthesis time is 45±5 minutes and the radiochemical yield is 20±5 % (n=3, without any decay correction). This does not include the trial batches to standardize the amounts and volumes of the starting materials, the temperature and time of reaction of S_N2 substitution, hydrolysis conditions as well as purification column.

[^{18}F]-FMISO can be successfully synthesized using a general purpose fluorination module and suitable reaction conditions. The novel indigenous purification column works satisfactorily to achieve the desired RCP and the whole process can easily be adapted in a commercial FDG synthesis module.

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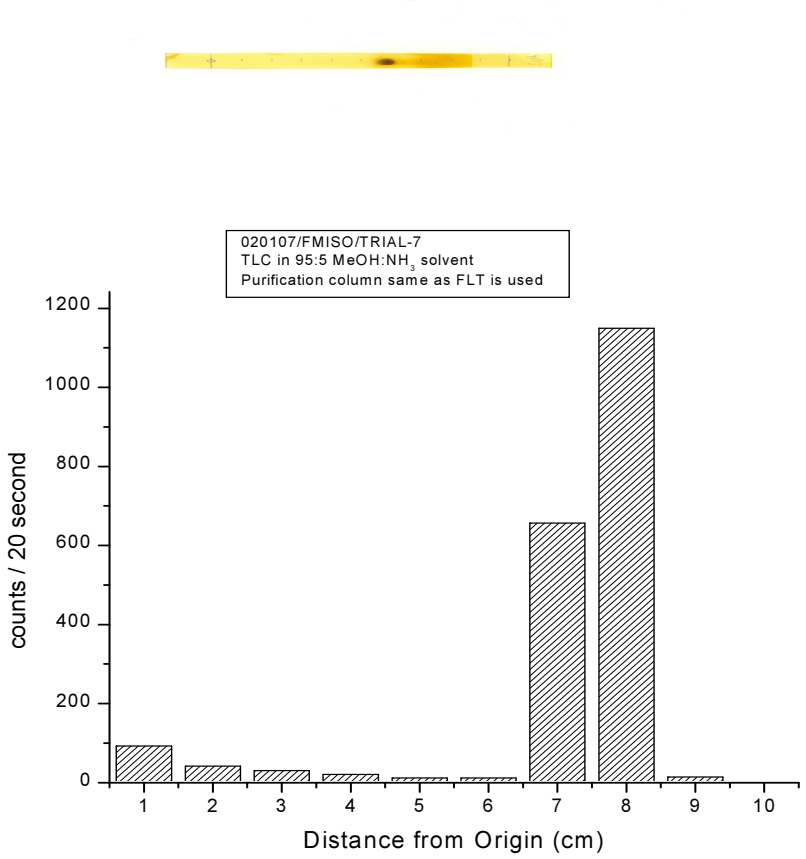

FIG. 1. TLC of [^{18}F] FMISO and Reference. ^{19}FMISO in MeOH: NH3 (95:5).

The potential of PET cyclotron installations for the production of uncommon positron emitting isotopes

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Positron emission tomography (PET) has become worldwide a standard clinical tool. Today several hundreds of PET cyclotrons are installed world wide in order to meet the still growing demand of PET-radiopharmaceutical, mainly FDG. Once the main task of a new PET cyclotron centre is fulfilled there is usually sufficient proton beam capacity available in order to produce other useful isotopes as well. Historically we can summarize, that the 80's was the phase for gas target development and -optimization while the 90's are characteristic for the optimization of the liquid target technology. Today intense R&D is undertaken to develop systems for solid target irradiation, that are needed for producing un-common or "new" isotopes with PET cyclotrons. In principle there are two general approaches for solving the problems. The first version is to replace the window foil of a classical water target system by a solid target coin that is than efficiently cooled by water from the rear side and with He at the front side. The second option is to irradiate the solid target material under declined conditions, which allows to distribute the beam over a larger area for better cooling. Both versions reached some technical performance. The Compact Solid Target Irradiation System (COSTIS), that has been developed along the first version is now commercial available from IBA.

In Tab. 1. a selection of interesting radionuclides are listed, which are in principle available in reasonable yields at PET cyclotrons. Most of them can be produced using the COSTIS installed on virtually any compact medical cyclotron. The target material has to be deposited on a suitable target coin; the target station provides He cooling for the front face of sensitive target materials and intensive water cooling at the target backing [1]. Commercial production of ^{124}I based on this technology is already underway in several PET centers providing 1-3 GBq batches depending on irradiation time. In order to recover the radioiodine from the irradiated targets an automated module for thermochromatographic processing (TERIMO) has been developed, which is commercially available from HWM. This module provides for automated, remotely controlled and GMP compliant radioiodine production, while the targets can be reused immediately after processing [2]. The total recovery of the produced radioiodine is typically 85 – 90%. The same technology may be used for producing ^{123}I in batches of almost 10 GBq of a radionuclide purity comparable to that obtained from the ^{124}Xe (p,2n) process. This is due to the today available extremely high purity enriched ^{123}Te target material (enrichment > 99.95%). Investment costs for the complete ^{123}I production technology along this line are less than 10% of that needed for the ^{124}Xe-technology.

Preliminary experimental data showed that one can also have access to the Auger electron emitter ^{165}Er [3], one of the very few isotopes that decay exclusively by EC, without accompanying gamma emission. The ionic radius and the physico-chemcial properties of Er are very close to that of Y or Ho. Thus, the same bioconjugates and the labeling procedures used for Y, Lu or Ho can be used without modifications for ^{165}Er as well.

In addition the (p,2n)-reaction channel can still be used, when the p-energy of the cyclotron is around 15 MeV. An example is the ^{81}Rb, which logistic is difficult because of half life constrains.

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† Presenting author

TABLE 1. SELECTION OF INTERESTING RADIONUCLIDES AND THE POTENTIAL OF PET CYCLOTRONS FOR THEIR PRODUCTION

Isotope	T ½	Reaction	Batch size	Application
^{44}Sc	3.92 h	^{44}Ca (p, n) ^{44}Sc	20 GBq	PET, bioconjugates
^{45}Ti	3.08 h	$^{nat.}$Sc (p, n) ^{45}Ti	10 – 20 GBq	PET, bioconjugates
^{55}Co	17.54 h	$^{nat.}$Fe (p, n) ^{55}Co	0.5 – 1 GBq	PET, enzymes, vitamines
^{61}Cu	3.4 h	^{61}Ni (p, n) ^{61}Cu	40 GBq	PET, in-vivo dosimetry
^{64}Cu	12.4 h	^{64}Ni (p, n) ^{64}Cu	40 GBq	Therapy
^{67}Cu	61.9 h	^{70}Zn (p, α) ^{67}Cu	10 GBq	Therapy
^{66}Ga	9.4 h	^{66}Zn (p, n) ^{66}Ga	10 GBq	PET, in-vivo dosimetry
^{76}Br	16 h	^{76}Se (p, n) ^{76}Br	2 GBq	PET
^{81}Rb/^{81m}Kr	4.58 h	^{82}Kr (p, 2n) ^{81}Rb	0.5-1 GBq	SPECT, ^{81m}Kr-generator
^{86}Y	14.7 h	^{86}Sr (p, n) ^{86}Y	5-10 GBq	PET, bioconjugates
^{89}Zr	78.4 h	$^{nat.}$Y (p, n) ^{89}Zr	10 GBq	PET, bioconjugates
^{90}Nb	14.6 h	^{90}Zr (p, n) ^{90}Nb	10 GBq	PET, bioconjugates
^{94}Tc	4.9 h	^{94}Mo (p, n) ^{94}Tc	10 GBq	PET
^{110}In	69.1 m	^{110}Cd (p, n) ^{110}In	5-10 GBq	PET
^{120}I	1.35 h	^{120}Te (p, n) ^{120}I	10 GBq	PET
^{123}I	13.2 h	^{123}Te (p, n) ^{123}I	10 GBq	SPECT
^{124}I	4.15 d	^{124}Te (p, n) ^{124}I	1-2 GBq	PET, in-vivo dosimetry
^{165}Er	10.3 h	$^{nat.}$Ho (p, n) ^{165}Er	20 GBq	Auger therapy
^{186}Re	90.6 h	^{186}W (p, n) ^{186}Re	5 GBq	Therapy

Note: The batch size depends essentially on reaction cross section, but also on which target design can be used, on the availability of target material (enriched or natural, cost) and how stable the target material is against the heat deposit of the p-beam and how long one can irradiate under practical conditions not disturbing the main task of the PET-cyclotron.

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PRACTICAL ASPECTS OF MULTIMODALITY IMAGING

PET/CT – Current status

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From autoradiography to planar X rays, Computed Tomography (CT) and Magnetic Resonance (MR), morphology and structure has been the mainstay of biological and medical imaging for over a century. While structural changes may suggest the presence of disease, functional changes are more sensitive indicators of early-stage pathology, and with cancer, early detection is the key to a favorable prognosis. Since molecular imaging offers the potential to quantitatively image functional changes *in vivo*, it is assuming an increasingly important role in the identification, staging and re-staging of human disease. Specifically, Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are sensitive techniques to map human physiology non-invasively through the use of high-resolution imaging devices and appropriate radioactively-labeled biomarkers. However, such metabolic maps do not offer the structural detail associated with anatomical imaging techniques such as CT and MR and therefore dual modality devices such as PET/CT, SPECT/CT or PET/MR that combine both structural and functional information offer a more complete and accurate assessment of the status of disease. PET/CT instrumentation, for example, was first introduced into the clinic in 2001 and since then, progress has been rapid. Technological advances in each modality, CT and PET, have been consistently incorporated into the combined device ensuring state-of-the-art performance for PET/CT. Recent advances in CT include an increase in the number of detector rows or slices (from 1 to 64), a reduction in rotation times (to less than 0.5 s), and the emergence of the first CT scanner incorporating dual X ray sources. Paralleling these advances, PET instrumentation has witnessed the introduction of new faster scintillators, higher resolution detectors, increased sensitivity through extended axial coverage, and the resurgence of time-of-flight information to improve image signal-to-noise. A major advance in image reconstruction techniques has been the introduction of statistically-based algorithms into clinical routine, with progressive refinement of the system model to more accurately represent the imaging process. Most of the independent advances in CT and PET instrumentation have been rapidly incorporated into state-of-the-art PET/CT designs and over the past six years, the development, introduction and rapid adoption of PET/CT technology has significantly impacted the medical imaging field. For oncology in particular, PET/CT has become the preferred imaging modality with over 1600 scanners now installed in clinical practice worldwide, progressively replacing PET-only tomographs.

The development of high performance CT scanners (64-slice and 0.3 s rotation times) has been driven primarily by cardiac applications. Lower performance CT (16-slice, 0.5 s rotation times) combined with state-of-the-art PET components will in general be adequate for oncology applications such as diagnosis and staging of malignant disease and monitoring therapeutic response. With the improvements in spatial resolution and sensitivity of PET instrumentation, the potential exists for earlier diagnosis and assessment of response to treatment when it can still make a difference for the patient. While FDG-PET/CT has provided incremental improvements compared to FDG-PET in both sensitivity and specificity for many clinical studies, some applications such as mediastinal and cervical lymph node detection still lack good specificity. There are, therefore, opportunities to further improve the sensitivity and specificity of PET, although such improvement is more likely to be achieved through the use of new, novel biomarkers than advances in PET/CT instrumentation. For cardiac imaging, the identification of plaque formation and other associated inflammatory processes is an important, although challenging, goal. The application of PET/CT to cardiology is still in its infancy as issues related to respiration and cardiac motion are addressed, and especially those arising from the use of CT-based attenuation correction in this setting. Mismatch between the CT and PET images can create artifacts that may have diagnostic consequences and therefore appropriate respiration and

cardiac gating strategies are currently being explored. The goal remains a single exam that can provide cardiac anatomy, angiography, perfusion and functional status of the myocardium. Incremental improvements and refinements in CT and PET instrumentation are to be anticipated in the future, including further increase in axial coverage, whereas major breakthroughs and insights are more likely to come from the introduction of novel PET biomarkers into clinical practice. Such biomarkers map physiological processes such as inflammation, cell proliferation, hypoxia, apoptosis and gene expression. As the specificity of these biomarkers increases, the requirement for the anatomical framework provided by CT will be essential. Thus, although currently the primary role of PET/CT is imaging FDG for oncology studies, the availability of other biomarkers will likely expand the use of PET/CT despite challenges from other developing hybrid modalities such as PET/MR.

Development in SPECT technologies

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Update on clinical SPECT/CT applications

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Nuclear medicine procedures produce highly specific functional data of physiologic and pathophysiologic processes but lack precise anatomic landmarks for better localization of suspicious foci of increased radiotracer activity. Co-registration of scintigraphic data obtained from SPECT procedures with anatomic information provided by CT has evolved from visual side-by-side comparison, through the use of software algorithms, to the technology of SPECT/CT. Hybrid imaging enables to perform sequential acquisition of SPECT and CT in a single session using the same imaging device. Transmission CT data are used for attenuation correction as well as for anatomic mapping of SPECT data [1]. Over the 8 years since its initial implementation into clinical practice the incremental value of SPECT/CT has been demonstrated in the assessment of a multitude of patient management settings in oncology and endocrinology, as a tool for diagnosis, staging, monitor response to treatment and follow up.

Imaging plays an important role in the evaluation of cancer patients, assessing different anatomical and functional aspects of tumor pathology. Co-registration of these two data sets improves interpretation accuracy and further clinical management. The interpretation of nuclear medicine studies can be, at times, difficult and inaccurate. Evaluation of differentiated thyroid carcinoma using I-131 is commonly problematic due to the characteristics of the tracer. Radioiodine scintigraphy lacks anatomical delineation and precise localization is therefore difficult to achieve. SPECT/CT fusion precisely localizes increased focal I-131 uptake and defines its significance [2,3].

Somatostatin receptor scintigraphy (SRS) provides information on functional status and receptor expression of neuroendocrine tumors. SPECT/CT improves the performance of SRS by detection and precise localization of small foci of disease and by excluding the presence of tumor in sites of physiologic tracer uptake [2,4].

SPECT/CT has been also reported as having an added role in other cancer-related clinical settings such as bone metastases, colorectal and prostate cancer investigation using labeled antibodies and in identification sentinel nodes using lymphoscintigraphy [1,5].

With advances in surgical techniques for parathyroid adenoma (PTA), precise localization of functional Tc-MIBI avid lesions has become of clinical significance. Diagnosis and localization of a PTA is particularly challenging in patients with ectopic disease, with recurrent hyperparathyroidism and distorted post-surgical neck anatomy, as well as in cases where the thyroid gland is not visualized in the early phases of Tc-MIBI scintigraphy (e.g. after thyroidectomy or following radioiodine treatment). SPECT/CT can precisely localize the PTA and define its relationship with surrounding organs, thus facilitating planning of the surgical procedure [2,5,6].

Initial studies, including however, large number of patients, indicate the potential role of SPECT/CT in the evaluation of infection. Fused images using Gallium-67 and labeled leucocytes improve diagnosis and localization of an infectious process since merging of complementary information of structure and function can overcome many of the limitations inherent to each modality. It has been demonstrated that SPECT/CT leads to improved diagnosis and subsequent optimized treatment planning, with a significant impact on clinical management and patient care [7].

In cardiac imaging, SPECT/CT provides state-of-the-art X ray based attenuation correction for myocardial perfusion scintigraphy with proven higher diagnostic accuracy in patients (mainly obese)

with ischemic heart disease. Combined with multislice CT, it is currently under evaluation for additional clinical applications beyond improving the image quality of cardiac SPECT studies. Pioneering research using a SPECT/multisliceCT device has demonstrated the feasibility of CT-based evaluation of coronary anatomy in the same setting with SPECT perfusion images. SPECT/CT defined the hemodynamic significance of non-invasively detected coronary occlusions [8,9].

A high quality SPECT/CT study requires a reliable, well functioning device which is regularly monitored for quality of performance. The study must be designed to answer the specific question asked by the referring physician and the patient must be appropriately educated and compliant. The technical staff must be well trained to perform and monitor the study according to a well-defined protocol, and the acquisition and processing protocols must be carefully followed. The images must be interpreted by skilled readers aware of the clinical history. High quality SPECT/CT studies consistently provide useful diagnostic information for the clinical management of patients. It is expected that as the quality of SPECT/CT devices improves, new applications will emerge.

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Combined PET – CT and PET – MRI imaging from non hybrid cammeras: Protocol approaches and clinical experience

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Like most Latin-American countries and developing countries over the world, Argentina have had a very fluctuant but small annual budget for public and private hospitals, limiting resources for updating, or upgrading used equipment in a regular basis like high cost hybrid PET-CT or SPECT-CT. Still, the information that combined diagnostic modalities offer is unique, determining the exact site of radiopharmaceutical concentration both in physiological and pathological situations. Physicians find that this sort of "fused" imaging lead to a more accurate treatment for patients. Moreover, the information obtained from CT images gives the information radiologists need for morphologic diagnosis. In our experience the combined imaging modalities (metabolic and structural) gave usually more information than the sum of individual modalities, not only for diagnosis but increasingly, in planning radiotherapy and surgery.

To be able to have adequate complementary information from two or more modalities, a correct integration of the obtained data from different scanners is mandatory.

The first step on this process is to align on space images from the involved modalities. This step is known as REGISTRATION. The following step, known as FUSION, is the display of both images at once with independent colour scales, melted in variable proportion for each scale.

In this presentation, we describe our experience with different approaches on PET–CT and PET–MRI alignment and display, analysing the performance of all the registration tools available at the Nuclear Medicine School Foundation, the impact of those tools and the necessary troubleshooting during implementation. Those tools include the development of our own software for automatic registration with different algorithms, and the use of available commercial ones from several branches. We found registration using fiducial or anatomical landmarks are unacceptable for clinical practice. Manual regristration is feasible, though is time consuming, and needs to be performed by trained staff, preferably checked or performed by the reader at the reading room. Authomatic Registration has today more acceptance. The method of choice in mutual information, described elswere [1]. It needs little training for software manipulation and no anatomical familiarity from the operator. Currently, the author's preference is to have a mutual information registration runned, and personaly check and correct manualy minor intermodality discrepancies while reading each study.

It is important to keep in mind that software performance depends on the known "garbage in, garbage out" concept, making necessary to put every effort on patient position and the acquisition protocol. Positioning of the patient on each scanner is crucial, excluding for brain imaging:

a) The radius of the bed on different scanners makes body shape and distribution of organs to change, sometimes considerably. We use either a bed supplement made of low density polymer on the CT scanner's bed to reproduce the radius of the PET bed for clinical diagnosis, or a flat bed in both modalities for combined metabolic and structural radiotherapy planning.

b) Neck holders and skin markers aligned to scanner lasers were the best approach for neck imaging. We used a product called backlock from the radiotherapy department with variable results.

d) Breath holding for CT imaging protocol is not adequate for PET registration. Instead of the usual breath holding after full inhalation used by radiologists, we use a full exhaling-breath holding protocol for whole body scan on a spiral CT, since the diaphragm position is closer to the averaged diaphragm position obtained on PET scanning.

c) But most important, the effort of technologists from the PET department to reproduce patient position on both situations was the "*sine qua non"* condition for adequate registration.

From the clinical point of view, combined imaging have had different, though strong impact. Combined PET-MRI brain imaging was valuable for differentiating FDG uptake of normal gray matter from increased uptake of primary recurrent tumours, and for PTV definition for external beam radiotherapy planning, among other applications. On whole body oncology imaging, we found combined imaging to be useful on each region, depending on the histology of the cancer, the previous treatment and the specific medical question. As an interesting finding for example, localization of unknown primary tumours, in spite of being one of the fewest clinical requests in number at our center, combined imaging was of crucial importance on every case. On the other hand, being lymphoma the most requested for PET-CT, fusion was proportionally less important for taking a clinical decision. Overall, more than 3000 PET fusions have been done until date, with hundreds of studies that made a difference on clinical treatment.

We conclude that there is not only one method combining two modalities that best fit for every situation, giving satisfactory results to each question. The best result was obtained when focusing on a single region than in a whole body scan.

Some commercially available software for registration are not user friendly, or need time consuming efforts in format conversions, dissuading nuclear physicians from using them in a daily basis.

Even though PET – TC and PET – MRI registration from separate scanners is not as fast and straightforward as from the Hybrid ones, it may be similar on results, facilitate clinical interpretation and gives referral physicians easy to understand images and sometimes, unique information that wouldn't be feasible in separate imaging modalities.

Key words: Medical imaging, registration, fusion, multimodality, mutual information, PET, CT, MRI, protocols, cancer, tumour, planning.

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Justification of a whole body PET CT study in post-treatment assessment of nasopharyngeal carcinoma

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Aim: To identify the usefulness of a whole body PET/CT study in post treatment cases of carcinoma of the nasopharynx.

Methods: A retrospective analysis of 55 post treatment (6-8 weeks to 2 years post concurrent chemotherapy and radiotherapy) cases of carcinoma of the nasopharynx referred to our department for evaluation of treatment response was done. Uptakes at the primary site, local nodal uptakes and abnormal uptakes elsewhere in the body were noted by a nuclear medicine physician. The simultaneously obtained contrast CT (CECT) images were analyzed by a radiologist blinded to the PET/CT report. Comparison of the contrast CT and PET/CT reports were done with respect to the primary and local nodes.

Results: There was a concordance of PET/CT and CECT findings at the primary site in 44 of the 55 patients, 22 patients showing no disease and 22 showing recurrence/residual disease.

11 (20%)of the patients showed discordance with 8 patients showing abnormality on the CT but no uptakes on PET/CT study. 3 patients showed residual/recurrence disease with no morphological abnormality on the CT images.

20 patients showed local nodal recurrence both on PET/CT and CECT. In 5 patients PET/CT identified local nodal involvement where CECT showed sub centimeter sized nodes which were normal by the size criteria. 10 CECT showed involved nodes in the neck while PET/CT did not reveal any corresponding abnormality.

16 patients had distant metastases – 5 of these had distant nodal metastases only and 12 had metastases to distant organ in addition to distant nodal metastases.

Discussion: All the patients included in the study were in the stage I or II. They were treated with a concurrent Chemotherapy and RT with curative intention. Routine post treatment investigations include a regional contrast CT & a USG in cases of local neck nodes for guided FNAC.

The possibility of distant metastases in this group of patients with nasopharyngeal carcinoma is low. However the current observation is that quite a few patients progress along the natural course of disease in spite of regional treatment. There appears to be a need for a whole body evaluation. Hence a single study which evaluates the whole body like a PET CT study would be beneficial in restaging these patients.

Conclusion:
29% (n =16) of the patients showed distant metastases.

In addition to the above findings 20% of the patients benefited with additional information regarding the primary site in the nasopharynx.

As regards the loco regional nodal staging14.28% of the patients were upstaged and 28.57% of the patients were down staged by PET/CT in comparison with conventional mode of investigation namely regional CECT.

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PHYSICS QUALITY CONTROL AND PROTOCOL STANDARDIZATION

Protocol standardisation

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The rapid growth of PET (and PET/CT) as a medical imaging technology is almost entirely due to the use of [^{18}F]FDG in oncology. This success story of [^{18}F]FDG, an analogue of glucose, is based on both the metabolic behaviour of tumours and the characteristics of [^{18}F]FDG itself. Unlike phosphorylated glucose, phosphorylated FDG is not a substrate for further metabolism. Therefore, its uptake in tissue is essentially irreversible and proportional to glucose metabolism. As most tumours have increased glycolytic rates, they can be detected as areas of increased [^{18}F]FDG uptake. The relatively long half-life of ^{18}F and the irreversible uptake of [^{18}F]FDG guarantee a high signal to noise ratio, i.e. good image quality. PET with [^{18}F]FDG is now considered to be the most sensitive *in vivo* method for detecting metastases and its value in staging patients with a wide range of tumours is generally accepted.

A potentially even more important application of [^{18}F]FDG PET (and PET/CT) is its use for assessing response to therapy. As it has been shown that in many cases functional changes are visible prior to structural changes, it is likely that [^{18}F]FDG PET could provide a means to distinguish responders from non-responders at a relatively early stage during chemotherapy. This has two important implications. Firstly, it could be used as a tool in drug development, both as an (early) surrogate endpoint and as a means to fully assess a new drug in responders only, by excluding non-responders based on (early) [^{18}F]FDG PET results. Secondly, it could be used for optimising treatment in individual patients. Early assessment of response would enable an early switch to alternative treatment strategies in non-responders, thereby avoiding unnecessary toxicity of ineffective treatment and gaining time in initiating a potentially more effective therapy (if available).

Although, slowly, evidence is emerging that [^{18}F]FDG PET is valid as an early response marker, progress has been hampered by the fact that data have been acquired with a variety of data acquisition and data analysis techniques, making it impossible to perform valid meta-analyses for larger study populations. At present, [^{18}F]FDG PET is more or less accepted as an early surrogate endpoint in drug development studies. However, another step is needed before it can be used to individualise treatment in routine patient care. This will need the collection of data on larger patients cohorts using multi-centre trials.

Multi-centre studies require that methodology is standardised. The first initiative to standardise [^{18}F]FDG PET methodology was made by the EORTC PET study group, publishing recommendations for measuring response using [^{18}F]FDG and PET [1]. These recommendations covered several aspects: patient preparation, scanning protocols, methods of analysis, and definition of metabolic response criteria.

With respect to quantification, the EORTC was particularly concerned that all clinical PET groups would be able to adhere to the recommendations specified. The resulting minimum standard was defined as SUV corrected for body surface area (SUV_{BSA}). A correction for plasma glucose was not recommended. Firstly, its effect was thought to be small, as the recommendations prescribed that patients should be fasting for at least 6 hours. In addition, many groups would not have easy access to an accurate technique for determining plasma glucose and the simple glucose assays used by most clinical groups are not suitable as they would introduce too much variability.

The EORTC recommendations also specified that al least one centre should perform a formal comparison of above-mentioned semi-quantitative SUV results with those obtained from the more

quantitative Patlak analysis. The purpose of such a comparison would be to verify that, for the combination of tumour and drug under investigation, SUV provided results that were indicative of glucose metabolism.

More recently, the NCI has drafted new guidelines [2]. Although there are some differences and additions compared with the EORTC guidelines, there is substantial overlap. Again, a SUV approach was recommended for routine applications, whilst for phase I trials a comparison with the Patlak method was deemed necessary for SUV validation.

Both EORTC and NCI recommendations agreed that the same region of interest method for sampling a tumour should be used on subsequent scans of a patient. They also agreed that further studies are needed to define the optimal region of interest method. Standardisation is extremely important for comparing absolute SUV values between institutes [3].

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PET/CT instrumentation: Quality Assurance and Quality Control

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Improvement in quality assurance in Nuclear Medicine and in particular, in quality control of related equipment is a major field of interest of the International Atomic Energy Agency (IAEA). Several technical documents pertaining to scintigraphic imaging have been published and are being used as reference manuals by many professionals in the field (e.g., TecDoc 317, TecDoc 602, STI/PUB 1141). Positron emission tomography (PET) scanners and related performance assessment and quality control were not included in the previously published documents, as PET has been mainly a research tool, with limited worldwide distribution until the 90s. The tremendous role played presently by PET and PET/CT in whole-body oncology for lesion detection, staging and follow-up as well as the increasing role for PET in cardiology and neurology, associated with increasing reimbursement of multiple PET indications have prompted the need for updated guidelines specific to PET and PET/CT in terms of acceptance testing as well as quality control and assurance. The aim of this work is to present an overview of acceptance testing and quality assurance and control for PET and PET/CT.

The refinement of standardized performance measurements for PET scanners has been an ongoing process over the last 10 years. The initial efforts by the Society of Nuclear Medicine, further elaborated by the National Electrical Manufacturers Association of the Unites States of America (NEMA; USA), resulted in the creation of an initial standard, the NU 2-1994 document [1]. A parallel effort by the European Economic Community led to the publication of the International Electrotechnical Commission (IEC) Standard in 1998 [2]. Despite some similarities between these two standards, there were distinct differences in the way the performance tests were performed and the phantoms used. In 2001, the NEMA standards were updated to the NEMA NU 2-2001 standard [3] that was more in agreement with the IEC standards, although some differences still existed. The NEMA NU 2-2001 standard was created in response to several developments in PET scanner technology that had by then been introduced into clinical practice, in particular 3-dimensional imaging. The 3D scanning required the definition and standardization of oblique lines of response in the performance tests. Furthermore, the development and wide use of whole-body imaging required axially longer imaging phantoms. In this context, the new 70-cm long phantom with an off-center line source was a better surrogate of whole-body activity distribution since it included the influence of out-of-field activity. Finally, the introduction of image-quality tests that assessed the overall performance of the scanner using a torso phantom with out of field activity, allowed the performance of different scanners to be compared under more realistic conditions. Despite the improvements made, the NEMA NU 2-2001 standard does not address several aspects of recently introduced PET scanners such as the CT component, the accuracy of registration of PET and CT and significant natural radioactivity in the detector material. Furthermore, it is essentially designed for quality control by manufacturers,

although it can be used during acceptance testing of new equipment to compare to the vendor's published specifications.

In contrast, the guidelines that are presented in this work and that will be published shortly in a new TecDoc by the IAEA are intended for the user and do address the main deficiencies of the NEMA NU 2-1001 standard, regarding the CT component, the quality of PET/CT registration, the natural radioactivity in the detector material, as well as objective assessment of image quality. Once the instrument that is being tested passes all the acceptance tests, "benchmark tests" must be performed. These are a set of quality control tests that are performed in the same way as the routine quality control procedures. The "benchmark" tests should serve as a baseline for instrument performance and are used to evaluate subsequent quality control tests. They should also be used to evaluate instrument performance after major service and updates in software and must be repeated after upgrades in hardware.

This work provides guidance about the specifications and prerequisites for acceptance testing of PET and PET/CT scanners, including professionals to be involved, definition of applications, minimal required configurations and corresponding performance parameters as well as ancillary equipment. It also provides guidelines and detailed description of acceptance testing and routine quality control for PET and PET/CT scanners. This in turn should provide guidelines for routine quality control of PET and PET/CT scanners and a framework for setting reference values, tolerances and action levels. Following these guidelines would ensure operation of the scanner under optimal conditions that yield the best performance in routine clinical tasks that involve lesion detection as well as quantitation of radioactive concentration. Such tasks are crucial for early detection of lesions in whole-body oncologic PET as well as staging, follow-up and therapy monitoring. These tasks are also crucial for activity quantitation when assessing the response to therapy or quantitating uptake of a radiopharmaceutical. The same applies to other indications of PET/CT in cardiac, neurological and inflammation imaging.

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Simultaneous PET/MRI in breast cancer: Development of the technology

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The ability to acquire high resolution anatomical data as well as quantitative functional information in vivo is becoming an increasingly important factor in the diagnosis of disease. This has clearly been reflected in the recent use of combined PET/CT as a clinical diagnostic tool as well as in the in the availability of commercial PET and CT scanners. However, while PET can provide high sensitivity and high specificity functional information, CT exhibits poor soft tissue contrast, and also subjects the patient to a significant additional radiation dose along with dose received with PET. On the other hand, MRI provides excellent soft tissue contrast and anatomical detail, and does not subject the patient to any additional radiation dose [1-6]. Simultaneous PET/MRI imaging would provide the ability to acquire in vivo quantitative functional information and high resolution anatomical data in animal or human subjects. Simultaneous acquisition of PET and MRI data would also provide essentially perfect co-registration between the two images which is particularly important for tissues whose position and shape can change between sequential scans. (Examples are head and neck imaging, colon imaging and breast imaging). There are several other advantages to combining PET and MRI into a single scanner. There are:

- MRI can be used to correct for partial volume effects in the PET image
- It would be possible to perform functional MRI studies simultaneously with PET physiological studies
- It would be possible to perform magnetic resonance spectroscopy to identify chemical species while observing the distribution and kinetics with PET
- The high magnetic field of the MRI causes positrons to curl up, reducing their range, which improves PET spatial resolution

The approach is based on the technology used for the RatCAP conscious small animal PET tomograph which utilizes block detectors consisting of pixelated arrays of LSO crystals read out with matching arrays of avalanche photodiodes (APDs) and a custom-designed Application Specific Integrated Circuit. A version of the detector has been developed that is constructed of all non-magnetic materials that can be operated inside the MRI field. The combined result is a highly compact, low mass PET scanner that can operate inside an MRI magnet without distorting the MRI image, and can be retrofitted into existing MRI instruments. We have now been able to obtain simultaneous PET and MRI images of rat brain using this device. A coregistered image is shown in Figure 1. The PET image was acquired over a 30 minute period. This design is now being adapted to imaging the breast for the detection of small lesion**s.**

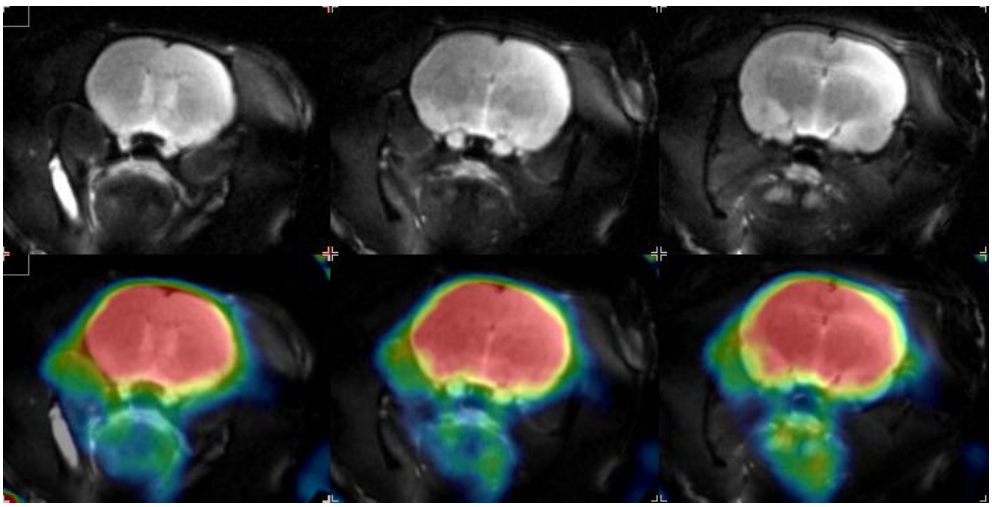

FIG. 1. MRI images and coregistered PET-FDG and MRI images of rat brain taken simultaneously.

The American Cancer Society is in the process of issuing updated recommendations that will include routine breast MRI screening for high risk patients based upon family history, genetic testing, radiation exposure history or high risk genetic syndromes. The addition of very high resolution positron emission tomography capability to an existing breast imaging system will give a device in which each of the modalities contributes its strengths to compensate for the weaknesses of the other. Although FDG-PET provides valuable information in terms of disease activity and extent of breast cancer, it offers limited anatomical information, which can cause inconclusive interpretations or mislocalization of the disease. MRI has low specificity in some instances and the potential for false positives that may lead to unnecessary procedures including biopsy. In this compact combined modality scanner, we have the anatomical information from the MRI to compensate for the poorer resolution in PET, and we have the predictive power of PET in identifying the type of lesion to overcome the high false positive rate of MRI. The very high resolution of this PET tomograph (which we estimate will be about 2 mm) will give a great advantage over the ability of whole body scanners to detect small lesions in the breast. The combined Breast MRI-PET images are likely to detect lesions not seen by other imaging methods and to better characterize lesions thus improving specificity of biopsy and reducing the number of unnecessary biopsies. The goal of this study is to investigate the feasibility for the product commercialization for a combined, compact and simultaneous MRI-PET imaging system based on a proven RatCAP technology developed by Brookhaven National Laboratory.

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PET in Argentina: A pioneer project in Latin America

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Aim/Background: This report describes in detail the work of planning, installation and operation for the first PET Center in Latin America. Situated in the city of Mendoza –1100 km west from Buenos Aires-, today it still represents a major challenge given the general infrastructure conditions and limited resources for the region. Our purpose is to share the experience of more than 15 years in this exciting field, so as to encourage and advise on the development of other PET facilities in Argentina and other countries.

The interest in Positron Emission Tomography in Argentina dates from the mid-80s, as an early initiative of CNEA (National Atomic Energy Commission) and its associated company INVAP (Applied Research Inc.). However, it almost took a decade to consolidate a working PET center at the Nuclear Medicine School Foundation in Mendoza (FUESMEN), and to develop its main constituents: radionuclide production, radiochemistry lab and scanning unit. Such areas are integrated by a multi-disciplinary team of physicists, engineers, radiochemists, technologists and nuclear medicine physicians.

Methods and Materials: The first stage in the development of our PET center was dedicated to building construction, equipment acquisition, installation, and experimental work with phantoms and animals. The main components are the PET scanner, a baby cyclotron (11 MeV protons) and a Radiochemistry Lab fully equipped with hot cells and FDG synthesis module.Quality assurance and scanning protocols were carried out from the very beginning. These initial steps were accompanied by a staff training program. All of the aboved mentioned professionals enhanced their knowledge at renowned foreign and national facilities. The International Atomic Energy Agency (IAEA) played a key role in the provision of equipment, sponsoring fellowships and expert missions, which were extremely beneficial for the project.

Results: Our facility is open for routine clinical studies since 1998, and it currently performs over 100 PET studies per month, an ever-increasing number. Patients are referred not only from other Argentine provinces, but also from neighbouring countries, although the request of foreign patients has been declining with the recent installation of other centers in Brazil and Chile. Approximately, 90% of the studies consist of whole-body scans with FDG (Fluoro-DeoxyGlucose) for Oncology, 5% brain scans and 5% heart studies using both ^{18}F-FDG and ^{13}N- Ammonia.

One factor that contributed to the prompt familiarization with PET were the previously achieved developments in conventional Nuclear Medicine techniques, such as Gamma Camera and SPECT (Single Photon Emission Tomography) in the same institution. Besides, the availability of other imaging modalities such as MR and CT and a in-house designed PACS (Picture Archiving and Communication System) helped to carry-out several image processing projects, in particular multimodal image registration and fusion.

Regarding radiation safety and quality control regulations, all staff and facility has to meet strong requirements in order to be qualified by the Nuclear Regulatory Authority (ARN), who considers the PET-Cyclotron center as a relevant facility. In addition, radiopharmaceutical production and delivery has to meet the demands of our National Food and Medical Technology Administration (ANMAT).

Back in the early 90's, research in Mendoza was oriented towards the quantitation of *in-vivo* metabolic processes in the brain and heart, according to the trends followed by other PET centers in the northern

hemisphere. Despite several promising (and sometimes evident) clinical applications, the PET technique would not yet find a place as common practice in Nuclear Medicine. A few years later, clinical FDG-PET boomed after it was widely accepted that it is not only a unique diagnostic tool in Oncology, but also becomes essential for patient management [1]. This new line of work produced an enriching interaction of PET physicians with the local radiotherapists and oncologists.

This close collaboration with the Radiotherapy Department is constantly growing, in particular for PET/CT assisted treatment planning. PET/CT registration is performed using in-house developed software. Currently, a new project in association with the IAEA aims at producing new labelled compounds, such as ^{11}C-Choline or Acetate for prostate cancer.

Discussion and conclusions: From our experience, and considering the high costs and complexity of a PET endeavour, the following issues should be paid most attention:

a) Design and execution of a continuing education program for all personnel.

b) Training of local engineers on corrective and preventive maintenance of the equipment. It is essential to keep a direct contact with the manufacturers, not just the local representatives.

c) Promotion of PET methodology and its benefits to referring physicians, radiologists, oncologists, insurance auditors and general public.

In conclusion, the expertise so gained facilitated the opening of new centers in Argentina. To date, at least five other institutions in Buenos Aires are doing clinical studies. Several others plan to do so in the near future, including the recently inaugurated PET/CT-Cyclotron center, perhaps the most rewarding outcome of years of pioneering work in Mendoza.

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Performance evaluation of a biograph 16 Hi-Rez PET scanner at King Chulalongkorn Memorial Hospital

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The performance characteristics of Siemens Biograph 16 Hi-Rez PET/CT system were measured using NEMA NU2-2001 standard. Its detector material was Lutetium Oxyorthosilicate(LSO).

Methods: The spatial resolution was measured by placing ^{18}F point sources at 1 cm and 10 cm radial offset from center of transaxial field of view. Images were reconstructed by using filter-back projection with all-pass, ramp filter. The sensitivity measurement, five sleeves aluminum tubes, sensitivity phantom inserted with line source was filled with ^{18}F solution. The phantom was acquired with 5, 4, 3, 2, and 1 cylinder at the center of transaxial field of view and 6.4 cm offset from center. The sensitivity values were estimated by extrapolating to the zero wall thickness. The scatter fraction and noise equivalent count rate (NECR) were measured. The scatter phantom with 70 cm length inserted with ^{18}F line source was centered in the transaxial field of view and coincidence count rates were acquired for 19 hours. The total number of acquired frames was 66 to obtain scatter fraction and NECR. The image quality was performed by using the International Electrotechnical Commission(IEC) body phantom set. It was filled with solution activity in spheres and background. The activity ratio was 8:1 (Sphere: Background). Contrast values were measured from a transaxial view which clearly seen image spheres.

Results: Transaxial spatial resolution at 1 cm and 10 cm offset from the center were 4.5 and 4.8 mm, respectively. Axial spatial at 1 cm and 10 cm offset from the center were 4.5 and 5.4 mm, respectively. Sensitivity values at 1 cm and 6.4 cm offset from the center were 4.8 cps/kBq@425keV. Scatter fraction was 30 percent throughout the clinical operating range of activity concentration. The peak NECRs for smooth randoms (k=1) and noisy random (k=2) corrections were 81 kcps at a concentration 26 kBq/ml and 57 kcps at a concentration of 23 kBq/ml. Contrast values of spheres were 25-72%.

Conclusions: The physical performance of this system was in the limit as compare with manufacturer's specification.

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F18- FDG-PET reconstruction: Slice thickness for optimal resolution

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For FDG-whole Body PET, as for any other medical imaging technique, resolution is a very important factor. In clinical practice however, most of PET centers use a 4mm pixel size reconstruction despite the fact that software for reconstruction with 2mm pixel size is usually available in the system. The reason is mainly practical, the processing time of 2mm reconstruction is 8 times longer than that of 4mm.

In this study we compare the results obtained using 4mm and 2mm pixel size reconstruction. The aim was to evaluate whether the improvement in resolution is obvious enough to justify a longer processing time.

Material and method:

PET camera:
All examinations were performed with a Gemini PET/CT system (Philips, Cleveland, USA). Reconstruction was performed using a 3D-RAMLA algorithm provided by the manufacturer.

Phantom studies:
Two phantom studies have been performed.

First, a Jaszczak phantom was filled with 2 mCi of F-18, and emission data were acquired in list mode for a total scan duration of 20 min. From the list mode data, both 2mm and 4 mm thick slices reconstruction were performed using data with different duration namely: 1 min, 2 min, 3min, 5 min, 10 min and 20 min.

A second phantom study was performed using 6 syringes with inner diameter varying between 2.65 cm and 0.48 cm, all filled with the same F-18 solution. The syringes were placed in the field of view of the PET camera and 20 minutes data were acquired.

Patients study: Data obtained in 22 consecutive patients were used. They fasted for at least 4 h before the examination to maintain serum glucose concentrations below 120 mg/dL. Scanning was started 45 min after intravenous injection of 400 MBq of ^{18}F-FDG. After a low-dose CT (20 mA, 140 kV, 512 x 512 matrix) covering the area from the vertex to the base of the skull a PET-scan was performed, emission data were acquired in 3 minutes per bed position. Scatter was first corrected then attenuation correction was performed using the CT-data. The reconstruction was done twice using respectively 4mm and 2mm thick slices.

The results were shown to 3 different observers who were asked to judge which reconstruction provide a better resolution.

Results: The results of Jaszczak phantom shows that for a 20 min data acquisition, the resolution obtained using 2mm thick slices is obviously better. It allows to visualize the 6.4 mm rods while 4mm thick reconstruction only allows to individualize 7.9 mm rods. This result is confirmed by the syringes study (Table 1). The partial volume effect is more severe when using 4mm instead of 2mm reconstruction.

For an acquisition time of 5 min both reconstructions visualize the 7.9 mm rods. For still shorter acquisitions and thus lower counts the 9.5 mm rods remain visual for both reconstructions but they become distorted for the 2 mm thick reconstruction.

TABLE 1. RESULTS OF ACQUISITIONS DONE ON JASZCZACK PHANTOM

Relative recovery count rate		
Inner diameter	4 mm	2 mm
2.65 cm	1.00	1.00
1.89 cm	1.00	1.00
1.44 cm	0.88	0.91
1.20 cm	0.63	0.76
0.86 cm	0.43	0.55
0.48 cm	0.15	0.21

Results of patients studies show that 4 mm reconstruction images are systematically smoother, hence less noisy but also less contrasted. As a whole however, the differences observed are minimal. In this series, no lesion was solely detected by one or the other reconstruction.

Conclusion: Our results indicate that 4 mm reconstruction is certainly not optimal, 2 mm reconstruction could provide a better resolution provided that a higher FDG dose is administered.

In the usual practical condition for FDG Whole-Body PET as described in this study: 400 MBq administered, 1 hour waiting period before scanning and 3 minute per bed position, the count rate is too low to take the advantage of 2 mm reconstruction.

PET NEUROLOGY

Brain tumor diagnostics using ^{18}F-labelled amino acids and PET

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Magnetic resonance imaging (MRI) has evolved as the most important diagnostic tool for assessing brain neoplasms due to its excellent soft tissue contrast and multiplanar reconstruction capabilities. However, a number of studies reported on dicrepancies between the real tumor extent and signal abnormalities in MRI. Encouraging results of improved imaging of tumor extent in cerebral gliomas have been reported with Positron emission tomography (PET) using radiolabeled amino acids such as ^{11}C-Methionine (MET).Due to the short physical half-life of the ^{11}C-label (20 min) MET PET remains restricted to PET centers with a cyclotron on site. Therefore, a number of attempts have been undertaken to label amino acids with ^{18}F (110 min half-life). O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) is one of the first ^{18}F-labeled amino acids that can be produced in large amounts for clinical purposes and is applicable for PET studies in a satellite concept similar to the widely used FDG [1].

In a prospective study we compared brain tumor imaging with FET PET in relation to MRI in 31 patients with suspected cerebral glioma. Biopsies were taken from lesions with abnormalities in MRI and increased FET uptake (match), as well as from areas with abnormalities in MRI but normal FET uptake (mismatch). MRI yielded a sensitivity of 96% for the detection of tumor tissue but a specifity of only 53%. The combined use of MRI and FET PET yielded a sensitivity of 93% and a specificity of 94% for the identification of tumor tissue demonstrating the potential of FET PET to detect the true extent of solid tumor mass [2]. Thus, the combined use of MRI and FET PET was clearly superior to that of MRI alone for the non-invasive distinction of tumor tissue and peritumoral brain tissue in patients with cerebral gliomas.

Furthermore, FET PET and Magnetic Resonance Spectroscopy (MRS) analyses were carried out on 50 consecutive patients with intracerebral lesions that were suspicious of diffuse gliomas on contrast-enhanced MR. FET lesion-to-brain ratio, and signal abnormalities on MRS were compared to histological findings in neuronavigated biopsy specimens. When both FET PET and MRS were negative, histology invariably failed to demonstrate tumor tissue. In contrast, a tumor diagnosis was made in 97% of the lesions positive with both methods [3]. Thus, in combination with MRS, FET PET yields extremely high sensitivity and specificity for the distinction of intracerebral tumors from non-neoplasic lesions.

No significant correlation was found between FET uptake in cerebral gliomas, the histopathological grading and the overal prognosis of the patients [1]. There appears, however, to be a prognostic role of FET PET in patients with low grade gliomas. We determined prognostic factors in 33 patients with untreated, non-enhancing, supratentorial low grade gliomas. Baseline FET-uptake and the pattern of a diffuse vs. circumscribed tumor in MRI were highly significant predictors of prognosis ($p < 0.01$). The combination of these two variables defined three prognostically distinct groups of patients with low grade gliomas. Assignment of the patients to these prognostic groups allows for an individually optimized and prognosis-related clinical management and therapy [4].

Other groups have investigated the potential of FET PET for the detection of recurrent gliomas [5]. Fifty-three patients with cerebral gliomas and clinically suspected recurrence after initial therapy were investigated by FET PET and the results were correlated with MRI /CT, clinical follow-up and biopsy findings. In the 42 patients with confirmed recurrences, there was distinct focal FET uptake with significantly higher values compared with those in the 11 patients without clinical signs of recurrence showing only low and homogeneous FET uptake at the margins of the resection cavity. Thus, FET

PET appears to be capable to differentiate between post-therapeutic benign lesions and tumor recurrence after initial treatment of low- and high-grade gliomas. The experiences with FET PET concerning therapy control are still scarce but initial studies indicated that FET PET is a valuable tool in monitoring the effects of chemotherapy and radioimmunotherapy [1].

The benefits of brain tumor imaging with FET PET or other radioloabelled amino acids are well documented and suggest an introduction of these methods into routine clinical practice.

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PET in epilepsy

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PET scanning in neurodegeneration

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Structural and functional images of the brain play an important role as useful adjuncts to the clinical symptoms in the diagnosis and management of neurologic and psychiatric diseases. There are various functional imaging modalities to identify functionally impaired, but morphologically preserved tissue and to distinguish it from irreversibly damaged tissue of the Central Nervous System. Functional imaging in general and Nuclear medicine in particular has a key role in diagnosing a variety of neurological disorders at an early stage. The key objective is to identify patterns of physiological abnormality which are predictive of pathology, which can then lead to earlier intervention in the patient's management. Brain SPECT, with perfusion agents or with neuroreceptor imaging radiopharmaceuticals, has become an important clinical tool in current practice. ^{99m}Tc-HMPAO SPECT is most useful in distinguishing Alzheimer's disease from vascular dementia and fronto-temporal dementia. ^{201}Tl- SPECT is an effective study in the diagnosis of CNS tumours. Altered dopaminergic transporter function in patients with Parkinson's disease is diagnosed using ^{123}I-ioflupane SPECT studies. This imaging modality has been used in diagnosis, prognosis assessment, and evaluation of response to therapy and detection of benign or malignant viable tissue.

Traditionally, PET scanning has been used as a research tool, and SPECT scanning using similar radioisotopes has been the more clinically applied tool. With the advent of PET-cT scanners for oncological use, and the development of newer tracers for various physiological functions, PET scanning in neurology is becoming increasingly acceptable in the clinical arena. Paraneoplastic Syndromes (PNS) have represented the bridge between oncological and neurological domains. PNS are recognised medical complications of cancer that cannot be attributed to direct effects of the neoplasm or its metastases. Paraneoplastic neurologic disorders (PND) can affect any part of the central or peripheral nervous system and often affect multiple areas simultaneously. One of the clinical hypothesis attributes PND to an autoimmune disorder precipitated by the immune response to cancer. In clinical practice, detection of neuron specific antibodies is crucial for the diagnosis because the neurological symptoms usually precede the diagnosis of cancer. Detection of the primary lesion at such early stages is often difficult but positron emission tomography has been shown to be a useful in identifying the lesion more accurately than the routine imaging procedures.

In neurology, PET provides significant clinical information for assessing various neurological diseases such as Alzheimer's disease and other dementias, Parkinson's disease, and Huntington's disease. The radioisotopes that are commonly used currently in PET are ^{18}F-FDG and ^{11}C-flumazenil. The new generation tracers include ^{18}F-DOPA, ^{18}F-Flumazenile, ^{18}F-MPPF, ^{18}F-Altanserine, ^{18}F-Methyltyrosine,^{18}F-Benzodiacepinreceptor, ^{18}F-Nicotinreceptorligands and O-Methyl-^{11}C-Raclopride.The severe hypometabolism noted in the different regions indicates diffuse neuronal dysfunction such as would be seen with dementia and other relevant neurological disorders. PET can localise epileptic foci for qualifying and identifying the site requiring surgical intervention. It also allows the characterization, grading and assessment of possible brain tumour recurrence.

It is important to remember that functional imaging of the brain is up against a bigger challenge when it comes to proving clinical usefulness. PET scans in other areas can be proved right or wrong on the basis of biopsy results. PET scans of the brain usually require some degree of post-mortem assessment to arrive at a decision on usefulness of the test. The continued use of research and clinical tools in parallel represents a good method of reassuring the clinical community of the usefulness of functional brain scans.

α-[11C]methyl-L-tryptophan as tracer for identification of epileptic foci using positron emission tomography imaging

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The proper identification of an epileptic focus is very often prerequisit for a successful surgical management of epilepsy. There have been great advances in the identification of epileptic foci by using modern imaging methods, namely positron emission tomography (PET) and magnetic resonance imaging (MRI). PET scanning with 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-FDG) has been used for presurgical evaluation of epileptic patient and identification of the fucus. An interictal epileptic focus is identified by the brain hypometabolic activity in the focus and surrounding brain area when 2-FDG and PET are used. These hypometabolic areas are often also identified by MRI when a structural lesion is present.

The greatest challenge is the identification of an epileptic focus when there is no structural lesion present or the identification of which lesion is epileptic when there are multiple lesions present (*e.g.*, multiple cortical despasia or multiple tuberoscleroses lesions). The proper identification of the area responsible for an epileptic discharge could greatly influence the outcome of surgical interventions. Elevated activity of the brain serotonergic system has been reported in brains with epileptic discharge. The use of ∀-[^{11}C]methyl-L-tryptophan (AMT) in conjunction with PET has been proposed as an imaging tool to evaluate brain serotonin synthesis in the living human brain. The method is based on the large volume of data obtained using laboratory animals and also using humans, where brain serotonin synthesis was modulated with the manipulation of substrates needed for serotonin synthesis (tryptophan and oxygen) or drugs known to affect brain serotonergic neurotransmission. In the normal brain, the kynurine metabolic pathway could be neglected, but it seems that in a pathology (e.g. brain ischemia, epilepsy) this pathway is activated. As result, the measurements with AMT in an epileptic focus represent the combined activity of the brain serotonin and kynurine synthetic pathways.

In experiments with dogs, we demonstrated that increases in blood oxygen and tryptophan result in increases of brain serotonin synthesis. It was also shown, in normal volunteers, that a decrease in blood tryptophan reduces brain serotonin synthesis, while an increase in blood oxygen results in an increase of brain serotonin synthesis. Fourty patients with intractible partial epilepsy were evaluated both with 2-FDG and AMT in addition to the conventional MRI. A subgroup of 18 patients that were evaluated with both MRI and 2-FDG did not indicate any abnormality. In ten of these patients imaging with AMT was able to identify an epileptic focus which corresponded to the foci identified by the scalp EEG. The AMT uptake in the epileptic focus correlated with the frequency of interictal spikes. The AMT imaging was also found to be beneficial in the patients with cortical displasia where, in four out of seven patients studied, the uptake of the tracer was observed. Eight patients with intractible partial epilepsy due to tuberous sclerosis complex were also imaged with AMT. In four out of these eight patients, there was an increase in the AMT uptake. Two of these patients showed a multiple foci of uptake while there was no significant uptake in the remaining two patients. An increase in the uptake of AMT in epileptic foci probably indicates a combined activation of the kinurinic and serotonin pathways of tryptophan metabolism. The data suggest that PET imaging with AMT is a promising diagnostic tool in the localization of epileptic foci and in aiding surgical management of these patients. Work supported by grant from the Canadian Institutes for Health Research and the National Institutes of Helaths (USA).

How FDG-PET helps making decision for surgery in various difficult subgroups of temporal lobe epilepsy?

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Background/Aim: Concordant pre-surgical data are the important predictors of good surgical outcome in patients with localization-related epilepsy. Medically intractable temporal lobe epilepsy with hippocampal sclerosis (HS) and concordant presurgical data is straightforward and may not need functional imaging. However, in other instances for example, HS with discordant data (HSD), bilateral HS with discordant data (BHSD), temporal lobe epilepsy with dual pathology (DP), non-lesional temporal lobe epilepsy (NL) are the difficult subgroups. In these groups, functional imaging eg. brain perfusion SPECT or brain PET may play a major role for surgical decision making. To our knowledge, there was no previous data in using FDG-PET in different subgroups as mentioned. Only some previous studies in single subgroup without analyzing impact of PET findings on decision-making have been reported [1,2,3]. We thus aim to evaluate the usefulness of FDG-PET in these 4 subgroups.

Materials and methods: Interictal FDG-PET studies were performed in 19 patients. Surface EEG was monitored before and during FDG uptake period. PET/CT scan was performed 30 minutes after FDG injection. Images were interpreted using visual analysis and comparison with normal patient file in equivocal cases. Area(s) of hypometabolism on PET scan were compared to data from clinical semiology, ictal EEG, interictal EEG, and MRI. The usefulness of PET in term of helping confirmation of possible ictal onset zone was analyzed. Concordance with at least 2 pre-surgical evaluation data, or concordance with ictal EEG, or focal area of abnormality in PET in whom other pre-surgical data were non-localizable, were identified as a helpful data for decision making.

Results: There were 8 HS with discordant data (HSD), 8 bilateral HS with discordant data (BHSD), 2 temporal lobe epilepsy with dual pathology (DP), and 1 non-lesional temporal lobe epilepsy (NL). Of all patients, PET helped confirm location or lateralization in 10 of 19 patients. In subgroup analysis, PET was helpful in 5/8 (62.5%) of HSD, 3/8 (37.5%) of BHSD, 1/2 (50%) of DP, and 1/1 (100%) of NL.

Discussions: PET is more helpful in HSD than BHSD because if there is unilateral temporal hypometabolism or even bilateral hypometabolism with more severe on 1 side, this can lead to conclusion of the possible side of ictal onset. In contrary, in BHSD, there is a more possibility of bilateral hypometabolism or even hypometabolism of contralateral temporal lobe to other pre-surgical data, which may lead to a non-helpful data. In DP and NL, PET showed focal hypometabolism that was confined to one lobe in some patients and was useful for decision-making.

Conclusions: PET is more helpful in temporal lobe epilepsy with unilateral HS and discordant data than bilateral HS and discordant data. In dual pathology and non-lesional epilepsy, if PET scan shows confined hypometabolism, it is also helpful.

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PET CARDIOLOGY

Cardiac metabolism imaging

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The use of substrate-specific radiotracers like C-11 palmitate, C-11 acetate, radiolabeled glucose analogs, and O-15 oxygen with PET permits the qualitative, and even more importantly, quantitative assessment of the myocardium's substrate metabolism.[1] Investigations with these radiotracers and PET have succeeded in delineating the normal human heart's substrate metabolism and its responses in substrate selection to changes in plasma substrate and hormone levels as well as to pharmacological stress. Other studies have demonstrated age- and disease- related effects on the myocardium substrate utilization as well as on the efficiency of substrate utilization relative to generation of contractile work.[2-6] Clinically most relevant has been the application of cardiac metabolism imaging to the assessment of the potential reversibility of contractile dysfunction (also called "myocardial viability") in patients with ischemic cardiomyopathy.[7,8] In dysfunctional myocardial regions with diminished blood flow at rest, potential reversibility is reflected by a sustained increase in the regional myocardial extraction of glucose. Myocardial viability as identified by cardiac metabolism imaging is highly predictive of the increased risk of cardiac death and morbidity in patients with ischemic cardiomyopathy on medical treatment.[9-11] Conversely, such metabolically defined myocardial viability in patients with ischemic cardiomyopathy is predictive of an improvement in long-term survival, in congestive heart failure related symptoms, and in left ventricular function after successful coronary revascularization.[9-12]

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Cardiac perfusion imaging

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Introduction: Measurement of regional myocardial perfusion plays an important role for evaluation of the physiologic significance of coronary lesions and adequacy of collateral supply. These myocardial blood flow measurements are often essential for characterizing the functional significance of coronary artery disease and are complementary to coronary angiography. PET measurements of myocardial blood flow reserve and endothelial function are useful for the serial evaluation of patients with the goals of determining the response to therapy and progression of disease. Current PET technology has spatial resolution of 4-6 mm and accurate attenuation correction permitting measurement of myocardial radiotracer concentration at frequent time intervals. Integration of PET instrumentation with a computed tomography (CT) scanner (PET/CT) can provide the means for accurate attenuation correction of myocardial perfusion imaging (MPI) and coronary arteries anatomical information in a single setting. Suitable kinetic modeling has been developed for several PET flow tracers and makes possible the accurate measurement of tissue blood flow.

The commonly used PET blood flow tracers can be divided into inert freely diffusible tracers such as O-15-labelled water and physiologically retained tracers such as N-13 ammonia and rubidium-82 (Table 1).

TABLE 1. PET MYOCARDIAL BLOOD FLOW TRACERS

Pharmaceutical	Radioisotopes	Half-life	Positron Energy (MeV)
Rubidium	Rb-82	76 sec	3.15
Water	O-15	110 sec	1.72
Potassium	K-38	7.6 min	2.7
PTSM	Cu-62	9.8 min	2.94
Ammonia	N-13	10 min	1.19
Acetate	C-11	20 min	0.96
Butanol			
FBnTP	F-18	110 min	0.63

Clinical Applicatons:

1) Diagnosis in coronary artery disease

Due to higher resolution with greater count density and attenuation corrected myocardial perfusion images as compared to the convetional SPECT, PET provides high diagnostic accuracy for detecting coronary artery disease.

Recently, the Canadian Cardiovascular Society has conducted a systematic literature review for Rb-82 and N-13-ammonia PET MPI in CAD diagnosis. The mean sensitivity and specificity of PET MPI are

89% and 89% with ranges from 83 to 100% and 73 to 100% in 14 studies including a total 1460 patients.

Although stress perfusion abnormalities can be identified with conventional SPECT in the majority cases, the interpretation of PET perfusion images is less equivocal, possibly due to the better quality images.

2) Prognosis in coronary artery disease

Defining prognosis in patients with suspected or known coronary artery is important in clinical care. In an early report using ^{82}Rb, PET perfusion imaging results were independent predictors of cardiac death and total cardiac events. The results of PET perfusion imaging yielded incremental prognostic information in comparison with clinical and angiographic findings alone. Importantly, ^{82}Rb PET also seems to have prognostic value in patients whose diagnosis remains uncertain after SPECT MPI and obese patients

3) Assessment of myocardial flow reserve

Quantitative measurements of myocardial blood flow reserve with PET MPI provide noninvasive means to determine the functional severity of coronary stenosis. While coronary angiography defines stenosis severity on the basis of morphologic alterations, the measurement of myocardial blood flow or flow reserve represents a more physiological evaluation of cellular perfusion as the net result of antegrade epicardial coronary flow and collateral circulation. Significant relationship was noted between the severity of relative perfusion abnormalities on PET perfusion images and coronary flow reserve measurements from quantitative coronary angiography.

A number of risk factors associated with atherosclerosis may cause reduction of coronary flow reserve despite angiographically normal coronary arteries. PET has been extensively used to investigate the relationship of coronary flow reserve and such risk factors for coronary artery disease, including hypercholesterolemia, diabetes, smoking, and hypertension. In addition, quantitative PET study is valuable for monitoring various treatments.

5) Assessment of coronary endothelial function

Coronary endothelial dysfunction is one of the earliest abnormalities to be seen in the development of CAD. Endothelial dysfunction is considered to be associated with future cardiac events. Schindler et al. evaluated prognostic value of myocardial blood flow response during cold pressor test using PET MPI (34). The blunted blood flow response was associated with cardiovascular events, and trend to be independent cardiovascular event risk factor. Altered endothelial function was associated with various plasma inflammatory biomarkers in patients who had coronary risk factors without overt coronary stenosis.

Conclusions: PET perfusion imaging provides accurate evaluation of regional myocardial blood flow at rest and during stress. The role of PET myocardial perfusion imaging is now well established for diagnosis of coronary artery disease. Recent data have shown prognostic value of PET myocardial perfusion imaging in patients with suspected coronary artery disease. In addition, PET perfusion imaging is the most validated noninvasive method for quantification of absolute myocardial blood flow、myocardial flow reserve and coronary endothelial function. The ability of PET to quantify absolute perfusion provides a new dimension in addition to the traditional applications of standard perfusion imaging. Thus, PET is also well suited for the evaluation of functional severity of coronary lesions and also monitoring various treatments for reducing cardiac risk factors.

Imaging peripheral vascular disease

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Myocardial uptake of 18F-FDG in wholebody PET studies

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Background: Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) is widely used to detect malignancy. The objective of this study was to study the degree and frequency of increased myocardial FDG uptake in routine oncologic PET studies and to correlate it with patient related factors like fasting blood sugar level (FBSL), fasting period (FP) and age of the patient that may have an influence on this phenomenon. Literature reveals many reports with controversial results on this subject.

Methods: We evaluated the data of 91 non-diabetic patients with malignant diseases who were referred for wholebody FDG-PET studies. There were 62 males and 29 females whose mean age was 43 years (range: 7-78 years). Patients were asked to fast for more than six hours before the test. Wholebody FDF-PET study was carried out after one hour of intravenous injection of 10 mCi (range 8- 12 mCi) 18FDG. GE Advance dedicated PET Camera was used for the study. Emission scan was followed by transmission sacn with 68Ge pin sources. Reconstruction was performed online using OSEM algorithm. Qualitative analysis of the images was carried out by experienced Nuclear Medicine Physicians. All patients were classified into four grades of myocardial uptake according to the visual interpretation of the FDG image: No myocardial uptake = Grade 0; Mild uptake (equivalent to normal liver tissue) = Grade 1; Moderate uptake (>liver but < brain) = Grade 2; and Marked uptake (equivalent to brain) = Grade 3. Quantitative analysis was done by calculating SUV max. Estimation of FBSL in all patients was done prior to injection of FDG. Total fasting period and age was noted by making inquiry with the patient.

Results: Thirty-seven (41%) patients showed no uptake in myocardium (Gr-0). FP, FBSL and Age was 14+/-3.05 hrs, 94.19 +/-11.9 mg% and 44.3 years (range: 16- 68 years) respectively. Eleven (12%) cases were rated as Grade I, 27 (30%) as Grade II and 16 (17%) as Grade III. The values of FP, FBSL and age were 12.9 +/- 2.47 hrs, 96.55 +/- 12.7 mg% and 43.54 years (range: 16-70 years) for Grade I, 13.48+/- 3.27 hrs, 87.11 +/- 9.03 mg% and 40.85 years (range: 7-78 years) for Grade II and 13.37 +/- 2.25 hrs. 86.56 +/- 12.73 and 36.18 (range: 11-66years) for Grade III respectively. SUV max was found to vary between 1 and 22.

Discussion: FDG-PET is a metabolic imaging modality, which is widely, used in the management of various diseases especially cancer. When exploring cardiac FDG uptake may interfere with the interpretation of images. Normally myocardium utilizes free fatty acid, glucose and lactate but under fasting conditions plasma insulin levels fall resulting in reduced transport of glucose into myocardium. In present study we found that 47% (Grade II&III) patients had significant cardiac FDG uptake inspite of blood sugar levels 71-125 mg%. In this study of 91 patients degree of myocardial FDG uptake did not show significant correlation to blood glucose level, fasting period or age which was in agreement with Michel de Groot et al. [1]. In a similar study Tomohiro KANETA et al. found a significant relationship between blood glucose level and heart FDG uptake [2]. They showed a negative correlation. Depending on our findings, a reasonable explanation may not be obtained. Heart metabolism is a complex phenomenon and FP, FBSL and age may probably not be the factors playing the role.

Conclusion: As the results of this small group of patients indicate, it is difficult to predict the degree of physiological uptake of FDG in the myocardium from the data regarding fasting period, fasting blood sugar level or age of the patient. Probably it is more a patient specific factor or some other

factors like insulin levels, medical treatments, and fat metabolism and myocardium status. It needs further exploration including a large number of patients and factors simultaneously.

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Determination of regional myocardial blood flow by ^{82}Rb PET imaging

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Abstract: The purpose of this project is to improve calculation of myocardial blood flow (MBF) in ^{82}Rb PET imaging using the wavelets temporal smoothing. 12 normal volunteers were imaged at rest, with 2220 MBq of ^{82}Rb each. A GE Advance PET system was used to acquire studies. MBF was calculated with a 2-compartmental model. The same set of images was analyzed twice in order to investigate repeatability. The results show high repeatability for global MBF with a value of 5.2%. For regional and average MBF, the repeatability was in the range of 27.9% for Apex_Lateral area to 2.6% MID_Sep-A area, which are marginal to good repeatability values.

Aim/Background: PET imaging has ability to provide noninvasive regional absolute quantification of myocardial blood flow (MBF) [1]. The purpose of this project is to improve calculation of MBF in ^{82}Rb PET imaging using the wavelets temporal smoothing.

Methods and materials: 12 normal volunteers were imaged at rest, with 2220 MBq of ^{82}Rb each. A GE Advance PET system was used to acquire dynamic 50 frame studies. The time per frame was 5 sec between 0-3 min, 15 sec between 3-5 min and 30 sec between 5-8 min. MBF was calculated with a 2-compartmental model using the PMOD program (PMOD Technologies Ltd, Switzerland) [2]. The same set of images was analyzed twice in order to investigate repeatability. The repeatability coefficient was calculated as 1.96 times the SD of the differences, and data are reported as mean ± SD. For better comparison, the repeatability coefficient is also given as a percentage of the average value of the 2 measurements.

From the short-axis slices, the PMOD program defines VOIs over the right ventricle (RV), left ventricle (LV) blood pool and over the LV myocardium with pointers defining the septum. The PMOD program defines 16 standard segments and calculates myocardial flow for each segment, as well as average septal, anterior, lateral, inferior and global flow.

Results: The results are given in Table 1. They show high repeatability for global MBF with a value of 5.2%. For regional and average MBF, the repeatability was in the range of 27.9% for Apex_Lateral area to 2.6% MID_Sep-A area, which are marginal to good repeatability values.

TABLE 1. REPEATABILITY OF MYOCARDIAL BLOOD FLOW CALCULATONS

Segment	Average Flow	SD	Repeatability	Repeatability%
SEPTUM	0.46	0.12	0.02	4.06
APEX_Sep	0.47	0.15	0.02	5.06
MID_Sep-I	0.49	0.14	0.03	6.03
MID_Sep-A	0.45	0.13	0.01	2.62
BASAL_Sep-I	0.46	0.17	0.03	5.54
BASAL_Sep-A	0.43	0.16	0.09	20.56
ANTERIOR	0.64	0.11	0.03	5.15
APEX_Ant	0.65	0.15	0.03	4.61
MID_Ant	0.63	0.09	0.03	5.42
BASAL_Ant	0.66	0.14	0.04	5.77
LATERAL	0.69	0.29	0.09	13.12
APEX_Lat	0.72	0.23	0.06	8.80
MID_Lat	0.68	0.24	0.19	27.91
BASAL_Lat	0.68	0.46	0.05	7.46
INFERIOR	0.79	0.30	0.06	7.24
APEX_Inf	0.82	0.36	0.11	14.00
MID_Inf-P	0.83	0.38	0.06	7.44
MID_Inf-I	0.91	0.61	0.05	5.85
BASAL_Inf-P	0.76	0.51	0.05	6.83
BASAL_Inf-I	0.71	0.45	0.05	6.64
GLOBAL	0.63	0.13	0.03	5.18

Discussions: Among PET MBF tracers only ^{82}Rb is generator-produced and therefore more affordable than other tracers, e.g., $^{13}NH_3$, and ^{15}O-labeled water. However, there are several issues related to quantification of regional MBF using ^{82}Rb. First, high positron energy (3.15 MeV) results in relatively poor resolution. Second, there is heavy dependence of the myocardial extraction of this tracer on the prevailing flow rate and myocardial metabolic state. Third, due to the short half-life of ^{82}Rb (78 s), cardiac images tend to be count-poor. Therefore, in order to provide accurate and reproducible results for global and regional MBF it is necessary to apply temporal smoothing.

Conclusion: When the wavelets temporal smoothing is used, the measurement of MBF with ^{82}Rb images shows very good repeatability for global MBF and marginal to good repeatability for regional MBF.

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SPECT IN THE PET ERA

SPECT and PET in paediatrics

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SPECT and PET are useful tools in paediatrics as well as in adults, improving the sensitivity and the diagnostic accuracy. Both techniques have a special interest for the the correlative image, improving the clinical usefulness of both metabolic (SPECT and PET) and anatomic images (MRI, CT, US).

SPECT in paediatrics

SPECT tomographic images are useful in most of the paediatric fields, but specialy in oncology, neurology, orthopaedia and cardiology.

In **paediatric oncology**, SPECT images obtained after the injection of metabolic tracers as MIBG, sodium iodine or octreotide allows us to detect residual tumour (neuroblastoma, thyroid tumour or carcinoid). SPECT increases the sensitivity to detect small lesions, lesions closed to bigger tumours, deep lesions or lung metastasis of osteosarcoma.

Radioguided surgery is an emerging field in Nuclear Medicine. In Paediatrics, SPECT and SPECT-CT (or SPECT-MR) are **useful** to assist the surgeon to localize residual tumoral mass (neuroblastoma, thyroid cancer lymph nodes) as well as radioguides biopsy (lymphoma).

The usefulness of brain SPECT in **paediatric neurology** is well known. Brain SPECT images are routinely used to localize epileptic foci, but also for a better understanding of most of the neuropsychologic paediatric diseases (brain death, trauma, vascular diseases, encephalitis, brain maturation, language disorders, obsessive-compulsive disorder, attention deficit disorder-hyperactivity, etc.).

In **benign bone diseases**, like Perthes disease, osteoid osteoma, bone infection or bone fractures, SPECT images improve the sensitivity and accuracy of bone scan and white blood cell scintigraphy. The tomographic frames, alone or fused with CT or MRI, provide important clinical information refered to the lesion extension or localization (v.g. radioguided surgery for an optimal removal of the nidus in osteoid osteoma).

In **nephrourology**, the benefit of SPECT images compared to DMSA cortical renal scintigraphy is not well accepted by most of the authors, specialy because it represents an increase of the injected dose.

Paediatric cardiology not only needs always the use of tomographic techniques but also an improvement in the acquisition parameters: zoom, immobilization, reconstruction parameters. The main applications during childhod are cardiac and pulmonary shunts, abnormal coronary **artery and** lung transplantation.

PET in paediatrics

Paediatric malignancies are the main indication of PET-CT in **paediatrics**. Compared to the adult population, **evidence based** indications for PET and PET-CT in paediatrics are difficult to rise due to the low incidence rate of paediatric malignancies. **However**, there is a high impact of this exam on the oncologic management of the paediatric patients

More and more papers have been published demonstrating that FDG PET/CT is also useful in children. Results obtained in paediatric lymphoma patients have shown high rates (up to 23%) of therapy changes owing to FDG PET results, and several recent papers have described the usefulness of

this technique in most other paediatric malignancies, such as neuroblastoma and sarcomas. Diagnostic accuracy is improved using fused PET-CT or at least side by side comparison of PET and CT images.

Remarks: Although in some areas of Nuclear Medicine it is feared that the mingling of functional and anatomical imaging procedures coming from the Radiology world could threaten Nuclear Medicine, this as speciality is being reinforced by the rapid expansion of SPECT and PET/CT. The use of **newer** tracers, both in oncologic and non oncologic illnesses foresees an interesting future for this Nuclear Medicine area.

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SPECT oncology imaging

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Although positron emission tomography (PET), especially with ^{18}F-FDG, has become the major radionuclide based technique for cancer imaging there are several tumor types where single photon emission computer tomography (SPECT)-based imaging is the method of choice. Furthermore, the development of SPECT scanners combined with diagnostic CT has improved the value of SPECT based cancer imaging.

With focus on neuroendocrine tumors, SPECT imaging of somatostatin receptors with ^{111}In-Octreotide and of the noradrenaline transporter with ^{123}I-metaiodobenzylguanidine (MIBG) will be reviewed. Based on our own studies of gene-expression in gastro-entero pancreatic (GEP) neuroendocrine tumors it seems unlikely that ^{18}F-FDG PET would be successful as a routine imaging techniques for these tumors indicating that specific tracers are needed. In addition, the potential added value of CT for SPECT-based oncology imaging will be discussed.

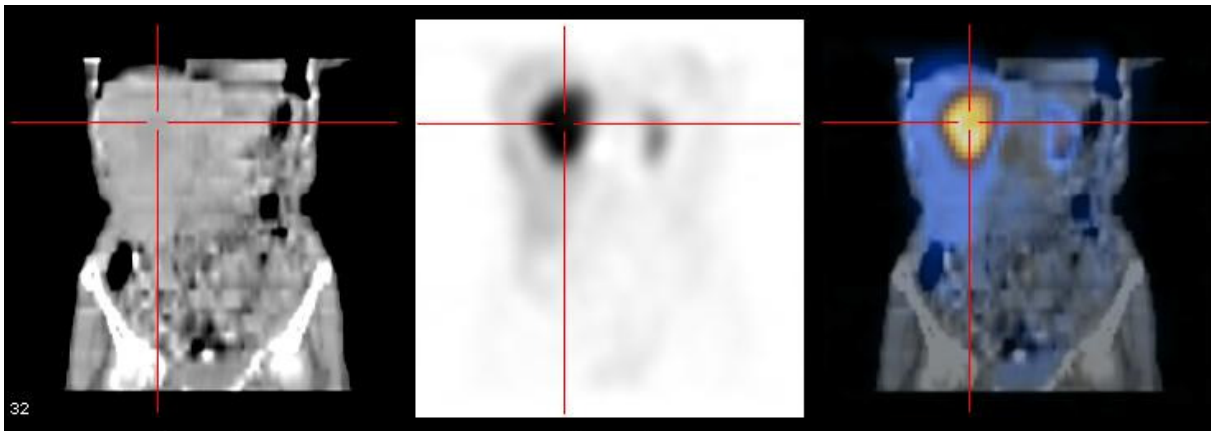

FIG. 1. SPECT/CT images of neuroendocrine tumor (VIPoma) in the liver. CT (left), somatostatin receptor scintigraphy with 111In-Octreotide (center) and fused SPECT/CT images (right).

Neuroendocrine tumors may be treated successfully with beta-emitting radionuclides coupled to somatostatin receptor ligands (*e.g.* ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC). Therefore, there is a close coupling between imaging and treatment based on somatostatin receptor over-expression in these tumors. Accordingly, SPECT based imaging in these tumors may be used for treatment selection, dosimetry calculations and prediction of therapy response.

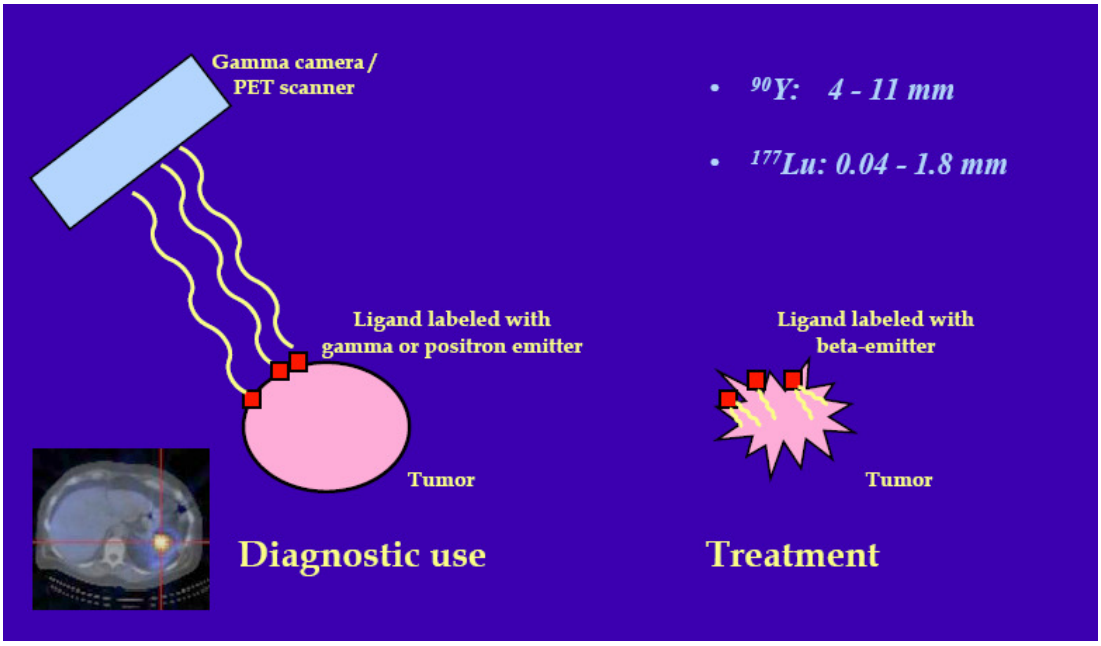

FIG. 2. Illustration of the close connection between imaging ligands and radionuclide treatment. Through selection of radionuclides the range of beta-radiation may be controlled.

In conclusion, SPECT/CT and PET/CT imaging supplement each other and should both be available for diagnosing, treatment planning and monitoring in oncology. SPECT/CT has an important role in the diagnostic work-up and for treatment planning in neuroendocrine tumors.

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SPECT metabolic imaging

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Myocardial Metabolism: Glucose and free fatty acids are two major energy sources in the myocardium. While fatty acid oxidation is most efficient for energy production, this process requires a large amount of oxygen. Therefore, under hypoxia or ischemic condition, oxidation of long chain fatty acid is greatly suppressed, whereas glucose metabolism, requiring less oxygen consumption, plays a major role for residual oxidative metabolism. No more metabolism is observed in myocardial necrosis. Thus, alteration of fatty acid oxidation is considered to be a sensitive marker of ischemia and myocardial damage. On the contrary, persistence of glucose utilization is considered as a suitable marker of myocardial viability in the dysfunctional myocardium.

Occlusion-reperfusion canine studies with chronic ischemia suggested prolonged metabolic alteration over 4 weeks after 30 min of coronary occlusion which is associated with sustained myocardial dysfunction. Thus, metabolic imaging may be used to identify prior ischemic insult, as ischemic memory imaging. Iodinated fatty acid analog, such as iodinated fatty acid analog (BMIPP), plays an important role to identify the areas of prior ischemia.

Although FDG-PET has become widely used in clinical setting on the oncological patients, there seems to be little slot for cardiac applications. In this sense, SPECT has been expected to probe metabolic alteration in ischemic heart disease and other myocardial disorders in clinical setting. We would like to describe clinical applications of SPECT metabolic imaging using FDG and BMIPP.

FDG-SPECT Imaging: Accurate assessment of myocardial viability in patients with ischemic heart disease becomes increasingly important in selecting the subgroup which may require revascularization. Preserved FDG uptake in dysfunctional areas indicates a viable myocardium, which has been shown to predict not only the improvement of the regional and global functions after revascularization but also improvement of survival compared with patients treated with medical therapy alone.

BMIPP-SPECT Imaging: Iodine-123 is an appropriate choice for labeling metabolic substrates because of its chemical property for synthesis by halogen exchange reaction in replacing a molecular methyl group and wide clinical application in clinical practice. Thus, iodine-123 labeled fatty acids have received great attention for assessing myocardial metabolism in vivo.

In the clinical studies with BMIPP, a rapid and high myocardial uptake with long retention was observed after BMIPP administration with low background with low uptake in the liver and lung at 30 minutes after BMIPP injection. A high quality of SPECT images can be obtained with collecting myocardial images for approximately 20 minutes. Generally BMIPP uptake was similar to that of thallium perfusion. Therefore, BMIPP distribution is carefully assessed to identify regional decrease in tracer distribution as an area of altered fatty acid uptake and metabolism. Regional BMIPP uptake is also compared with regional perfusion to detect presence of perfusion-metabolism mismatch. A number of reports from Japan showing less BMIPP uptake than perfusion (discordant BMIPP uptake) often observed in ischemic myocardium.

BMIPP has also been used for risk stratification in patients with coronary artery disease, based on the concept that the areas with less BMIPP than perfusion may represent ischemic and jeopardized myocardium. This concept has come from the important prognostic findings reported on the perfusion-metabolism mismatch pattern on FDG-PET studies. Among various clinical, angiographic

and radionuclide indices, discordant BMIPP uptake was the best predictor of future cardiac events followed by number of coronary stenosis in the mean follow-up study of 23 months of 50 consecutive patients with myocardial infarction.

Conclusions: Alteration of fatty acid oxidation is considered to be a sensitive marker of ischemia and myocardial damage. On the contrary, persistence of glucose utilization is considered as a suitable marker of myocardial viability in the dysfunctional myocardium. While, FDG-PET is considered as a accurate means for assessing myocardial viability, FDG-SPECT using ultrahigh-energy collimators can provide similar information as FDG-PET with regard to viability assessment. The role of metabolic imaging for identifying post-ischemic insult as “ischemic memory imaging” has recently been focused. A number of reports from Japan showed quite acceptable diagnostic accuracy of BMIPP imaging for detecting coronary patients without prior myocardial infarction. In addition, the recent data indicates BMIPP imaging has a prognostic value when applied in documented or suspected coronary patients. In conclusion, SPECT metabolic imaging may play a new and important role for identifying prior ischemia and assessing the severity in patients with coronary artery disease.

Screening of asymptomatic patients with type 2 diabetes mellitus for silent coronary artery disease with stress myocardial perfusion imaging

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Introduction: Diabetes Mellitus (DM) predisposes people to premature atherosclerotic coronary artery disease (CAD). Diabetes increased the risk of CAD by a factor of 2–4 [1] which is the leading cause of morbidity and mortality in diabetic patients. The risk of myocardial infarction (MI) in diabetics without overt evidence of obstructive CAD matches that of patients without diabetes who have had a previous myocardial infarction [2]. Patients with DM had a high incidence of silent MI or ischemia [3-7]. Myocardial ischemia is a major complication in the course of diabetes, and 25% of patients with type 2 DM already have CAD at the time of diagnosis. About 22% of asymptomatic diabetic patients present ischemia in studies of stress myocardial perfusion [8]. The true incidence of silent CAD in diabetic population varied between 20% and 50% depending of the conditions of the patients, presence of risk factors, age, gender, duration of diabetes. Because of the prevalence of CAD in the diabetic population and its overwhelming burden of early mortality, careful evaluation of CAD risk is crucial. Is recommended by different groups as the American Diabetes Association (ADA) and the American College of Cardiology, to performed cardiac testing not only in diabetic patients with symptoms indicating the presence of CAD but also in patients with possible anginal equivalents and in asymptomatic patients. Several studies have demonstrated the utility of Myocardial Perfusion Imaging (MPI) as a useful tool for diagnosing significant CAD in diabetic patients and for risk stratification and management.

The purpose of our study was to examine the prevalence of silent ischemia by MPI in asymptomatic patients with DM type 2.

Population and Methods: We considered all consecutive asymptomatic patients (n=104) with Type 2 diabetes Mellitus referred for MPI. A survey considering age, gender, angina and or chest pain, previous AMI, cardiac revascularization, smoking, hypertension and dyslipidemia was done.

We performed a conventional 1 or 2 days protocol using Tc-99m Sestamibi. Pharmacological stress was done with dypiridamole in a dose of 0.57 mg/kg. Administration of nitroglycerin sublingually about 3 minutes before rest injection of the radiopharmaceutical was done. Phillips Forte dual-head gammacamara with high-resolution collimator was used to acquire 64x20 sec projections along 180º, non-circular orbit with heads at 90º from another. ECG gating for the acquisition of cardiac function was used.

Visual analysis of rest and stress images and semi-quantitative analysis of polar maps of MPI was done, using 17-segment nomenclature. Infarction was diagnosed when there were no changes between stress and rest MPI. Ischemia was defined as reversible perfusion abnormalities. Left ventricular ejection fraction (LVEF) was calculated by gated SPECT.

Statistical analysis was done using SPSS version 13.0 and logistical regression analysis. Statistically significant was $P < 0.05$.

Results: Among 104 asymptomatic diabetic patients, they were 89 males and 15 females. The average age was 66.7±10.9 years old.

Eighty three of them did not have CAD and/or previous AMI. In this group of patients 19 (24.7%) had ischemia in the MPI. LVEF at rest was 43.7% and 58.3% in the group with ischemia and without ischemia, respectively ($p<0.001$)

Ischemia was found in 13 out of 21 (61.9%) patients with previous history of CAD but asymptomatic at the time of MPI. There were no significant differences in LVEF between patients with previous CAD with or without ischemia.

There were no association among risk factors of CAD and the presence of ischemia at MPI.

Discussion: This paper is the first one in our country which analyses the presence of CAD in asymptomatic patients with Type 2 DM. Our results, similar to others authors, showed that the prevalence of ischemia in this group is frequent; 24.7%, eventually candidate for medical treatment and eventually revascularization. In spite that there is not fully agreement regarding the useful of routinely screening for CAD, we recommended the use of MPI in asymptomatic patients with type 2 DM.

One of the problems in our analysis is that we did not registered the duration of the disease and complications secondary to DM. In the other hand, over 80% of the patients were studied as part of a presurgical evaluation.

Conclusion: Screening for silent CAD is absolutely justified in asymptomatic patients with diabetes because of the intermediate prevalence of CAD and its significant morbidity. MPI is a useful tool for diagnosing significant CAD in this group of patients allowing the evaluation of perfusion and ventricular function.

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The value of 99m-Tc octreotide SPECT to localise neuroendocrine tumours for successful surgical treatment

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Aim/Background: Many of neuroendocrine tumours (NETs) tumours are known to express somatostatine receptors with varying intensity [1]. $^{99m-}$Tc radiolabelled somatostatine analogue (^{99m}-Tc EDDA/HYNIC-TOC), with pharmacokinetic properties very similar to commercially available ^{111}In-Octreoscan® [2], was introduced as a new radiopharmaceutical for diagnosis and localisation of NETs. The proper therapy of solitary tumours is surgical one. Since NETs are small and frequently difficult to find intraoperatively, accurate preoperative localisation of the tumour is of paramount importance [3].

The aim of the study was to determine the usefulness of ^{99m}Tc radiolabelled octreotide SPECT for the success of surgery of NETs.

Materials and Methods: 16 patients with clinical and biochemical evidence of NET were investigated. 6 patients were previously nonsuccessfuly operated for NET. Scintigraphy was done using 550-650 MBq of Octreotide, labeled as D-Phe1, Tyr3-octreotide with 99m-Tc [4] in house. SPECT and planar scintigraphy were acquired 1 – 2 and 3 – 4 hours after injection. The uptake by the tumor was graded according to the EANM Guideline (1), on the scale from 0-4. Conventional morphologic diagnostic methods (CDMs): CT, MRI, endoscopical US were also performed in all patients. Gamma probe was used during surgery to facilitate detection of NETs (radioguided surgery).

Results: In 16 patients altogether 17 NETs were localized; in 16 cases as a solitary lesion, while one patient had two tumours identified.

12 NETs were found during radioguided surgery and removed. There were 5 carcinoids, 3 neuroendocrine carcinomas 2 gastrinomas and 2. insulinomas. The surgeons were able to localize 3 out of 4. lesions with grade 4, 7 out of 8 lessions with grade 3, and 2 out of 3. lessions with grade 2 uptake. In all five patients with tumour in upper abdomen (bifurcate of aorta, mesentery, illeocecal region, next to aorta) and in 7 out of 12 patients with tumour in the area in or next to the pancreas the probe localization and removal of the tumours was sucessful. According to CDM the size of the succesfully removed tumors and those not found was virtually the same (mean size 17 vs. 18 mm). Two NETs in 2 patients clearly seen on octreotide SPECT were not seen on any CDM.

In all patients where tumor was removed, except one, there was no clinical, biochemical or scintigraphic evidence of NET on the 6 months follow-up. In one patient the recurence of the tumour was seen on 99m-Tc octreotide SPECT in the same region.

Discussion: According to our results 99m-Tc Octreotide SPECT is the most sensitive method to localise solitary NETs, suitable for surgery. CDMs are less succesful an also less specific but nevertheless essential for planning of the surgery [1]. Additionally 99m-Tc labeling of the octreotide makes radioguided surgery possible [5]. Surgical localisation of the NET is obviously more successful in case of high uptake of the trace and localisation of the tumor away from organs with normal high tracer uptake (spleen, kidneys and possibly liver). The histology and size of the tumor had no influence on the succces of the surgery.

Conclusion: Use of ^{99m}Tc radio labelled octreotide SPECT is a useful help to localize NET. In patients with high octreotide uptake (grade 3 or 4) 99m-Tc octreotide SPECT, especially if combined with gamma probe during surgery has decisive role in localising NETs even in cases when morphological investigations are negative.

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PRESENTATIONS AND PANEL DISCUSSION:

TRAINING & EDUCATION

Issues on training of physicians/technologists

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With the rapid advances of technology and radiopharmaceutical development training must be constantly adapted to meet the necessary quality standards. According to a recent survey of the European Association of Nuclear Medicine (EANM) Board exams are requested for nuclear medicine physicians in 21/28 European countries, in 9 and 8 countries for physicists and radiopharmacists, respectively and 14 countries for technologists. Furthermore, the European Board of Nuclear Medicine organises each year a European Board exam that confers the title of European fellow to European specialists in Nuclear Medicine who have successfully passed the written and oral parts of these exams. In recent years this exam has been made available also to colleagues from non-European countries that by passing the exam are attested that their knowledge and ability fulfils European standards.

Concerning the content of training, the revised version of the syllabus, is a condensed catalogue of training requirements, has been published in the European Journal of Nuclear Medicine (2007;34:433-436). It clearly states the scopes and limits of the medical specialty of nuclear medicine on which are based the formative objectives that include basic and specific theoretical, as well as integrative objectives. Finally the requirements in basic science and clinical training are enumerated. nuclear medicine is a complex speciality, which is characterised by extensive transversality asking for broad basic, clinical and technological knowledge. Training programmes must take this diversity into consideration.

The arrival of multimodality imaging, today PET and SPECT coupled to CT, tomorrow also to magnetic resonance scanners represent an additional challenge. It is the absolute right of the patient to have his/her imaging study interpreted by the most competent physician. It is, however, with the increasing workload not possible to have all PET or SPECT-CT studies interpreted by both, a specialist in nuclear medicine and a radiologist. Therefore training in multimodality imaging has to be provided. Several scenarios may be envisaged from complete dual specialty training to completely integrated training in both specialties, which will be chosen on the national level according to local conditions and legal requirements. In any case, nuclear medicine trainees must become acquainted, on top of in-depth training in nuclear medicine, with other cross-sectional imaging methods. Crossover training between nuclear medicine and radiology needs to be organised, the contents of training be defined.

Similar challenges expect nuclear medicine technologists who need to learn how to run hybrid imaging equipment under the aspects of patient safety, radioprotection and diagnostic quality. In many countries the decision had been taken to offer a common training or at least a common trunk to technologist who will then further specialise either at the end of primary training or during a postgraduate curriculum.

A great flexibility and capability to adapt to a changing environment are requested from both, nuclear medicine physicians and technologists in order to face, with the help of scientists in basic and applied sciences, the fascinating world of cellular and molecular targeting for diagnosis, disease characterisation, treatment response evaluation and finally treatment of benign and malignant diseases in close interaction with specialists trained in other imaging disciplines and clinicians.

Issues on training of radiochemists/radiopharmacists

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As the science of Positron Emission Tomography (PET) continues to expand, there are training issues that must be addressed for radiochemists and radiopharmacists involved in the production and delivery of PET radiopharmaceuticals (RaPh) for human use. PET RaPh are a unique subset of RaPh, due to the short half lives of the PET isotopes, which allow limited time for production and quality control. Also, PET isotopes require significant radioprotection due to the high energy emitted. PET RaPh typically contain low mass quantities ($\leq$ μg) of active ingredients, must be sterile products for injection, and are usually produced in hospitals or Cyclotron Centers. The regulatory framework for the production of these products varies greatly depending on the country, from full Good Manufacturing Practice (GMP) compliance to no enforcement of pharmaceutical regulations. Cyclotron Centers are often operated by non-pharmacists. Therefore, post graduate training specific for non-pharmacists is needed to be qualified for the preparation of RaPh. Some of the elements required include understanding of pharmaceutical formulation, legal aspects of producing medicinal products, understanding of pharmacopoeias, principles of aseptic and sterile productions, radiopharmacology, GMP and Quality Assurance (QA) systems management.

The European Association of Nuclear Medicine (EANM) has developed a post graduate Radiopharmacy and RaPh Chemistry Certificate Program for training a "Responsible Person for Preparation of RaPh" for both PET and non-PET RaPh, and has begun an initiative to have this cetificate accepted by the EU and its member states as appropriate qualification for those individuals managing radiopharmacy units, including PET. This certificate is available to anyone who completes a defined program of education and a two-year period of practical experience in the field. The program is coordinated by the chairman of the EANM Radiopharmacy Committee, and details are available on the web at http://www.eanm.org. It is taught in three blocks of two weeks and includes Pharmacy, Radiopharmaceutical Chemistry and Associated Subjects.

In the United Kingdom (UK), Kings College, University of London, UK, offers a Masters package (1 year full-time, or 2 years part-time), "Radiopharmaceutics and PET Radiochemistry," to train graduate chemists and pharmacists for employment and research in the radiochemistry/radiopharmacy associated with nuclear medicine and PET. The contact person for this program is Philip J. Blower (P.J.Blower@kent.ac.uk).

The Canadian Association of RaPh Scientists has developed a Training Program for the PET RaPh Sciences, and the faculty are from the University of Alberta. This post secondary education program provides training in nuclear pharmacy, nuclear physics, chemistry and radiochemistry as they relate to PET RaPh preparation. This course is intended to provide the skill and competency to prepare PET RaPh as well as providing an overview of Canadian legislation, PET radiopharmacy design, clinical controls and GMP issues and an introduction to PET RaPh research. The entire training course comprises approximately 75 hours. Information is available at http://www.radiopharmacycanada.com.

In the United States (US), the University of New Mexico and the Univerity of Arkansas Colleges of Pharmacy provide nuclear educaton online at http://www.nuclearonline.org The post graduate radiopharmacy education and training program is open to pharmacists and other professionals. It is intended to provide education and training required by the US Nuclear Regulatory Commission (NRC) to become an Authorized Nuclear Pharmacist or an authorized user of radioactive materials. The program length is 18 weeks, including didactic and experiential training. The program is in the process of developing training for PET RaPh production.

IAEA/RCA (Regional Cooperative Agreement for Research, Development & Training Related to Nuclear Science and Technology) provided a Regional Training Course on PET in 2005 for physician and scientist training. The course was offered at the University of Fukui in Japan. The course included training on accelerators, FDG automated synthesis overview, and quality control. Additionally PET Radiation Safety and PET applications were covered. Currenly there is a PET Summer Seminar, originally offered to Japanese physisists and chemists, which now provides training for PET physicians, technologists, cyclotron operators, and business personell. The 29th Annual Summer Seminar was held August 24-26 2007. The web address for the meeting is http://pet.jrias.or.jp/index.cfm/28,html.

As the use of PET RaPh continues to increase world-wide for medical use in diagnostics, disease staging, monitoring of drug therapies, new drug development and pharmakokinetic evaluations in industry, the need for trained personnel will grow. International efforts should be made now to evaluate the needs of countries developing PET technology, and encourage and support the development of appropriate training programs. Training opportunities, such as those described above, will greatly suport the growh of PET and encourage the development of new clinically approved molecular imaging RaPh.

Issues on training of medical physicists

G. El Fakhri

Meeting training needs in PET/CT; Extending DAT for the 21st century

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Background: As integrated imaging technologies develop rapidly there is increasing need to update the knowledge and skills of nuclear medicine professionals. With the recent explosion of PET worldwide an effective training approach is required to educate users located in diverse regions where teaching resources may be limited. Currently the IAEA are developing new training materials on the use of SPECT/CT and PET/CT focusing on the practical applications that follow clinical reasoning and applying rules for safety and quality assurance. Through utilization of interactive teaching software and internet resources it is anticipated this innovation will benefit technologists in particular, by promoting good techniques in everyday practice. Following the success of the Distance Assisted Training programme for nuclear medicine technologists (DAT) there has been a demand for new training modules to include PET and CT with a mechanism for ongoing refinements as protocols change and new technologies are introduced.

Method: The goal of DAT has been not only to produce training materials but also to assist in the implementation of training programs based on the materials. The material has been specifically designed to assist individuals to develop basic practical skills that enable them to perform good quality nuclear medicine studies. This flexible course attempts to provide a focus on factors which are important in clinical practice rather than, as in many courses, offering a very general theoretical coverage. It is hoped that this focus highlights the relevance of underlying theory so that students can understand the importance of what is presented and can better identify problems which may occur in their daily work. The same philosophy is extended into the new training modules.

Results: Over several years pilot studies to test DAT efficacy in the basic science, clinical and SPECT subjects have been conducted in 23 developing countries, with >400 technologists which resulted in translations to Chinese and Spanish. Following international reviews this sustainable program is being adopted as the national training program for nuclear medicine technologists in a growing number of countries around the world. It would seem appropriate to use this proven mechanism of course implementation for the ongoing training in new technologies. The same strategy of course design remains but media for course content delivery will be inline with technological advancements.

Discussion: The DAT materials are free of charge to countries that meet criteria of appropriate infrastructure, appoint a National Responsible Authority and follow IAEA guidelines for implementation. On successful completion students receive a National Certificate indicating grades of achievement in all categories. Important outcomes with DAT include a common basic standard of knowledge and practice and a comprehensive standardized assessment offering a new benchmark for competency based standards. The development of problem solving skills, improved self esteem and confidence are experiences reported by DAT participants thus stimulating a renewed interest in continuing education. Physicians and physicists in-training can also benefit from studying the materials. These attributes of the program suit the demands of PET/CT training and ongoing developments into the future.

Conclusion: DAT is a formalized structured training course offering a unique opportunity to harmonize global training in nuclear medicine and PET - there is no other course of instruction that meets this need.

PET: THERAPY PREDICTION/ASSESSMENT

Radiotherapy planning

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CT represent the current gold standard for radiotherapy planning (RTP). The development of *biologic imaging* brings new information about cancer. The modern images integrate many biologic aspects, including data on genotypic and phenotypic expression, metabolic activity, cell proliferation. These elements are very useful to draw more specific strategies for treating cancer. Nuclear medicine, with SPECT and in particular PET, offers significant contributions in defining the volume for treatment. This imaging is based on different radiopharmaceuticals, able to describe glucose metabolism, cell proliferation, angiogenesis, hypoxia. The nuclear medicine images can be co-registered and fused with CT and also MRI, and give both morphological and functional information, that are incorporated into RTP for a better definition of the target volumes.

The target volumes includes three concepts: the gross tumour volume (GTV), the clinical target volume (CTV) and the planning target volume (PTV).The CTV contains the GTV plus any regions estimated at risk of subclinical disease. The addition to the CTV of a margin representing the geometric uncertainties (set-up errors and organ motion) generates the PTV. The integration of nuclear medicine imaging into the RTP leads to a definition of a *new concept of target*, the *biological target volume* (BTV). According to the radiopharmaceutical used the BTV expresses different properties of the tumour. Bentzen et al has defined the term of "theragnostic imaging", the multimodality imaging keptas a guide for designing the highest dose spots in the context of the tumour. The difference between this concept and the morphological imaging is that it provides information to determine *how* and *not only where* radiation therapy should be delivered. The attention should be also focused on the functional aspects and the importance of healthy tissues so as to reduce the radioinduced damage. In conclusion the use of the multimodal imaging will lead to a *personalized* radiation therapy, biologically optimized *for the individual* instead of *for the population* of patients. The expected clinical result are the improvement of the loco-regional control, and consequently of the survival, with the lowest possible risk of severe iatrogenic complications.

The inclusion of FDG-PET in the RTP has for the first goal the improvement of cancer staging and the identification of the tumour volume, using the anatomic imaging as a frame for the calculation of the dose. This may have significant effects. The impact of PET on the target delineation is related to the accuracy of the study (diagnostic sensitivity and specificity) for the type of cancer to be treated. PET affects the treatment planning according to the requests from the radiation oncologists. If tumour missing is the major concern, the sensitivity is the strongest requirement and the interpretation criteria should be strict. On the contrary if the major purpose is tissues protection and thus their exclusion from high dose volume, the specificity becomes the most important parameter. Another advantage provided by PET/CT images co-registration is the reduction of the inter-observer variability in target delineation.

Besides the added value in defining PTV, the most promising use of multimodality imaging is the characterization of biochemical and physiological features of the tumour, and this can a guide for the delineation of tumour sub-volumes to be boosted. In this context, the benefit offered by the multimodal imaging makes the ideal match with Intensity Modulated Radiation Therapy (IMRT), because of its particular ability to *"paint the dose"* close to the selected volumes. For example if the intensity of FDG uptake is related to tumour burden, IMRT plan can be designed to deliver an additional dose in that area, to maximize the probability of a local control. While the dose escalation in metabolically active areas is still experimental, the use of FDG/PET for a more precise and accurate localization of the disease has entered into clinical use, at least for specified solid cancer types.

A further possibility offered by the metabolic imaging is the prediction of the responsiveness to radiotherapy during the early phase of treatment. Monitoring in a semi-quantitative way the reduction of FDG uptake (through SUV changes) can allow the optimization of the treatment and modify the strategy of the original plan, Another role of nuclear medicine in RTP is the definition of healthy tissues to be spared, instead of the tumour volumes delineation. Imaging can allow the identification of non-functional tissues and thus guide the beam set-up.

The use of multimodal imaging in the RTP requires several steps. First of all, the *image fusion*, that is the transfer of information from one study to another. The second step is the *image co-registration*, that gives a spatial mapping of the corresponding points of the images. The third step is the *delineation of the volume* based on a metabolic radiopharmaceutical uptake. In fact, although the nuclear physician makes the analysis mostly with a qualitative approach, the radiation oncologist needs *a quantitative evaluation*.

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Role of PET and PET/CT in the assessment of response to chemotherapy

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Introduction: Recent advances in chemo-/immunotherapy for the treatment of cancer have not only increased overall survival but also improved patients' quality of life. There is a need, however, to balance improved therapeutic success with possible associated risks and high treatment costs so that the net result is really beneficial ("individualized" or "tailor made" therapy) for the patient. The very high sensitivity of metabolic/molecular imaging for detecting disease at a very early stage was shown by Fischer et al. [1]. Based upon an average tumor cell size of 20 μm^2, PET (theoretically) allows visualization of a tumor volume of only 33.5 mm^3. Indeed, many clinical studies have demonstrated the high value of PET and especially of PET/CT for staging, restaging and follow-up of patients and to assess response to therapy.

Rationale: The tumor stage at diagnosis defines the prognosis of the patient. Tumor volume, heterogeneity of the tumor cell population, growth cycle of cells at which the therapy is started, blood supply and oxygenation of tumor tissue all significantly affect the outcome of therapy and all of these parameters are influenced by treatment. However, in current clinical practice (and also in research studies) only the tumor diameter in one or two dimensions (e.g., WHO and RECIST criteria) is taken into account for the evaluation of therapy response. Although patients with less than 10% residual tumour by volume after completion of therapy have an excellent prognosis, molecular imaging is needed for the early assessment of response, i.e. even before volume changes have occurred ("metabolism proceeds morphology"). Histopathology is currently the gold standard for the characterization of a tumor and for evaluation of the accuracy of imaging modalities. However, because of tumor heterogeneity, biopsy specimens do not always provide reliable results and often it is difficult (or impossible) to obtain a tissue specimen for histolpathological analysis. PET as a non-invasive, whole-body imaging modality can even surpass biopsy by detecting previously unknown tumor sites (e.g. detection of bone marrow metastases in the spine after a normal iliac crest bone marrow biospy). New imaging probes like tumor-specific peptides targeting receptors or antigenic sites may reach (nearly) similar specificity as a tissue specimen taken for histological analysis.

Clinical results: ^{18}F-FDG PET has been used extensively in monitoring response to chemotherapy in lymphoma, lung cancer, breast cancer and colorectal cancer. In patients with aggressive NHL, ^{18}F-FDG PET provides a more accurate response classification than International Workshop Criteria (IWC) alone[3]. In the revised response criteria for malignant lymphoma, ^{18}F-FDG PET is recommended as essential for the assessment of response in diffuse large B-cell NHL (DLBCL) and Hodgkin's lymphoma [4]. ^{18}F-FDG PET is useful for monitoring chemotherapy response in lung cancer [5] and PET/CT has high value in the assessment of response to induction chemotherapy in stage IIIA-N2 disease [6]. A multicentre study has shown that a simple visual assessment of mediastinal lymph node status on the PET scan predicted outcome whereas CT did not [7]. In breast cancer patients, ^{18}F-FDG PET was able to predict response to chemotherapy as early as after the first course [5]. Conventional imaging (CI) has been found to be inferior to ^{18}F-FDG PET in predicting outcome after completion of chemotherapy with positive and negative predictive values of 93% and 84% for ^{18}F-FDG PET, versus 85% and 59%, respectively for CI [8]. Systemic chemotherapy has been shown to double the survival of patients with advanced colorectal cancer as compared to untreated controls. Early response

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assessment of this highly potent and potentially toxic chemotherapy is necessary in order to increase its effectiveness without causing too much economic burden. ^{18}F-FDG PET and ^{18}F-FU PET can help oncologists and surgeons better manage colorectal cancer patients [5]. In sharp contrast to CT, ^{18}F-FDG PET is a very sensitive molecular imaging modality to evaluate an early response to imatinib mesylate (Gleevec) in gastrointestinal stromal tumors [9]. This is an exquisite example demonstrating that many of the new (and sometimes very expensive) "smart drugs" which are now in phase III clinical trials or already in clinical use are potential candidates for using PET to monitor therapy response at a very early stage.

Conclusion: Response assessment of chemotherapy using metabolic and molecular markers labeled with positron emitters, has opened a new chapter in monitoring patients and will be an essential part of optimizing therapeutic strategies and patients' management in the future [5].

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Prostate cancer - Assessment and therapy follow-up with PET

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In prostate cancer, there has been a long-standing need for better imaging methods, to localise the primary lesions, stage the cancer, and evaluate its treatments. Molecular imaging with positron emission tomography (PET) and the most recent PET/CT fusion are indicated to detect cancer tissue on basis of its abnormal metabolic properties, with higher diagnostic performance than both conventional radiologic imaging and conventional scintigraphy.

Fluorodeoxyglucose-(18F) PET or PET/CT

Fluorodeoxyglucose (FDG) is a glucose analogue designed for PET imaging. FDG PET has a recognised clinical utility in all the above settings of many major cancers (lung, colorectal, head and neck, melanoma, lymphoma, gynaecological cancers …). But FDG PET has not proven to be regularly useful in any clinical setting of prostate cancer. Although it is able to detect aggressive, advanced or metastatic prostate cancer [1-3], the primary lesion itself frequently does not show-up significantly [4,5]. For the detection of bone metastases, FDG PET is inferior to conventional bone scintigraphy [6-8] and its performances are poor in the detection of post-treatment recurrences [9] or recurrences responsible for rising prostate specific antigen (PSA) serum levels [10].

Fluoromethylcholine-(18F) PET or PET/CT

Fluoromethylcholine-(18F) or FCH is a PET imaging analogue of choline [11], a lipidic component of normal cell membranes which is produced in larger quantities in cancer cells.

Unlike FDG, FCH is also taken-up by low proliferating malignancies such as most of the prostate cancers. An accumulation of choline has been demonstrated in prostate cancer tissue by magnetic resonance spectrometry [12,13]. By comparing FCH PET and FDG PET in 18 patients with prostate cancer, Price [14] found more lesions in the prostate, bone, and soft tissue with FCH. The uptake of FCH by the cancer cells is so rapid that it is possible to get rid of the high regional background induced by radioactivity excreted in the urinary bladder, just by performing an early dynamic acquisition before FCH enters the ureters and the bladder. We therefore start CT and then PET acquisition just after injection of 4 MBq/kg of body weight of FCH (Iasocholine®, Iason). This dynamic acquisition lasts 8 min at a one frame per minute rate, over the pelvic area. A whole-body PET/CT image is subsequently acquired. Some author advice to wait for one hour before performing the whole body acquisition for a better visualisation of the bone metastases.

Assessment of prostate cancer with FCH PET or PET/CT

In many patients with high PSA serum levels, multiple prostate biopsies, the reference method to assess prostate cancer, are unable to localise the probable cancer. Using standard 6 or 12 needle templates is prone to sampling error, with a false negative rate as high as 20% regardless of the number of needles employed [15,16]. Furthermore, since nerve-sparing is considered an important therapeutic option in some patients undergoing prostatectomy, the ability to confirm the side affected by cancer may help determine which side to spare. In this context, MRI can be performed but is frequently non-contributive. FCH PET, and better PET/CT since it yields anatomical landmarks, has been proposed to guide further biopsies. Kwee [17] reported that in patients with biopsy-proven prostate cancer, the prostate sextants harbouring malignancy demonstrated significantly higher FCH uptake than biopsy-negative sextants. FCH PET correctly identified the affected side in all 6 patients with unilaterally positive prostate biopsies. Therefore, this information may help diagnosing prostate cancer by identifying the areas of the prostate which should be biopsied first. However, inflammation

and benign hyperplasia result in a non-specific FCH uptake [18]. Furthermore, lesions of prostate cancer are frequently bilateral, so it is important to obtain an accurate detection of the most active cancer lesions. We made the hypothesis that processing FCH PET/CT images with factor analysis may improve the localisation of the carcinoma tissue inside the prostate. In all cases, the first factor actually matched the anatomical landmarks of the urinary tract and thus the second factor was expected to delineate the cancer tissue; they respectively explained around 80% and 20% of the total variance. Confrontation with histology revealed that FA permitted in 3/8 cases (38%) to localise focal lesions of active cancer that could not be identified on 'raw" images. This was confirmed in larger preliminary series and FDG PET/CT was able to delineate the active lesions of prostate cancer even when diffusion MRI was inconclusive.

Therapy planning and follow-up with FCH PET or PET/CT

FCH PET/CT may prove useful for planning prostate cancer treatments. For example, using FCH PET/CT to define definitely malignant tissue, it may be possible to identify the dominant areas of malignancy within the prostate using FCH PET [19]. Guiding radiotherapy, or a combination of brachytherapy and external radiotherapy with PET/CT data, it may be possible to direct very high radiation doses towards malignant targets within the prostate while still treating the remainder of the prostate with a conventional therapeutic dose, in addition to maintaining an acceptable level of radiation exposure to uninvolved organs.

Although no formal study has been currently reported, FCH PET is useful in our experience for early evaluation of the efficacy of local therapies such as ultrasounds and to detect foci of viable cancer [20].

Recurrence of prostate cancer after radical treatment is a growing problem. "Biochemical" recurrences (PSA serum levels > 0,2 ng/mL) occur in around 40% of patients [21]. The patient's management is quite different according to the topography or the recurrent cancer tissue : focal local recurrence, diffuse recurrence in the prostate, locoregional recurrence or distant metastases. In particular, radiotherapy requires a precise delineation of targets [22,23]. Standard imaging consists of endorectal ultrasonography with biopsies and bone scintigraphy, which is rarely contributive when PSA serum levels are below 10 ng/mL.

Several studies have explored the relationship between lesion detectability with FCH PET/CT and PSA serum levels and in patients with suspected prostate cancer recurrence. A study by Heinisch [24] found that FCH PET/CT could identify cancer recurrences in only 41% of 17 patients suspected of having recurrent prostate cancer with PSA serum levels below 5 ng/mL. In a recent article by Cimitan [25], FCH PET/CT was able to identify confirmed sites of prostate cancer recurrence in 54 of the100 patients. In this study, 89% of the patients with non-contributive FCH PET/CT examinations had serum PSA levels below 4 ng/mL. Thus, FCH PET/CT appears less sensitive for the detection of recurrent prostate cancer in patients with low PSA levels (< 4 ng/mL), in particular when the initial Gleason score was below 8. However, it is worth noting that in both studies, the positive findings on FCH PET/CT provided enough information to help distinguish between local and distant metastatic recurrence.

As the determination of criteria that predict a reasonable chance of success for FCH PET/CT would have a major practical impact, we also tried to derive a possible threshold for PSA serum levels and PSA velocity and we evaluated whether PSA velocity would be a better selection criterion than PSA serum levels. Between May 2005 and April 2007, 106 FCH-PET were performed at Hôpital Tenon for suspicion of prostate cancer recurrence, based on a persistent increase in PSA serum levels. Patients had been previously treated by prostatectomy (n = 54), radiotherapy (n = 34), HIFU (n = 12), or brachytherapy (n = 6). PSA absolute and relative velocity (ratio between velocity and initial PSA levels) could be calculated in 49 patients. ROC analysis was performed to compare the ability of PSA and PSA kinetic parameters for selecting patients with positive FCH PET/CT, i.e. 58/106 patients (55%). Mean PSA levels and absolute PSA velocity were significantly higher when FCH-PET was positive than negative. High PSA absolute velocity permitted to select patients with PSA levels <

5,g/mL in whom FCH PET/CT was positive, while relative PSA velocity was of no help. A positive result for PSA PET/CT influenced patient's management significantly and in an appropriate manner.

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Therapy monitoring based on FDG-PET follow-up studies for the prediction of individual survival

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Abstract: Dynamic PET studies with ^{18}F-FDG were performed in patients with advanced Non-small Cell Lung Cancer (NSCLC) who received palliative chemotherapy to evaluate the impact of full kinetic analysis and assess its value with regard to short or long survival. Furthermore, we performed FDG-PET studies in patients (pts) with metastatic colorectal cancer receiving FOLFOX (5-fluorouracil, folinic acid and oxaliplatin) chemotherapy and evaluated different quantification methods for prediction of individual survival.

Methods: The evaluation includes 42 metastatic lesions in 14 patients with NSCLC. All patients received a combined chemotherapeutic protocol consisting of vinorelbin and oxaliplatin. The survival data served as reference for the PET data. All patients were examined prior to onset of chemotherapy and on day 15-21 after onset of the first cycle. Furthermore, 25 pts. with metastatic colorectal cancer who were scheduled for FOLFOX chemotherapy were studied. All patients were examined prior to onset of FOLFOX therapy, and after completion of the first and the fourth cycle.

The following parameters were retrieved from the dynamic PET studies: SUV, fractal dimension (FD), two compartment model with computation of k1, k2, k3, k4 (unit: 1/min), the fractional blood volume (VB) and the FDG-influx according to Patlak was calculated using the formula (k1 x k3) / (k2 + k3). We used a two group classification, namely a short and long term survival group based on the median survival time as a cutoff. A support vector machines (SVM) analysis was used for classification of the two a priori defined groups. Discriminant analysis (DA), regression and best subset analysis were applied to the data.

Results: NSCLC: The observed survival times varied from 40 to 392 days with a median survival time of 193 days. Most kinetic parameters demonstrated only small changes, mostly declining after one cycle. The change in all kinetic parameters did not correlate to the survival based classification.The change in SUV was significant between the first and second study (p=0.006) but without an impact on the prediction of short ot long survival. SVM based analysis revealed the highest correct classification rate (CCR) between short and long survival for the combination of SUV and influx of the first study and SUV, influx, k2, k4 of the second study with a CCR of 95.2%.

Colorectal cancer: Twenty of 25 pts died up to 801 days after the first PET study. A cutoff of one year (364 days) was used to classify the pts into two a priori groups, namely short and long term survival group. DA was used to predict the two categories using SUV and kinetic parameters of the FDG metabolism as predictor variables. SUV provided a correct classification rate (CCR) ranging from 62% to 69%. SUV of the third study resulted in a CCR of 69% as a single parameter. The best results yielded by the use of kinetic parameters (k1, k3, VB, FD) as predictor variables. CCR was 78% using

kinetic FDG parameters of the first and third study in comparison to 69% for the corresponding SUV´s. A multiple linear regression model was applied to the data to assess the relationship between the individual survival and the PET data. Best subset method revealed a correlation coefficient of 0.850 for the kinetic parameters of the first (k3, k4, VB, FD) and third study (k1, k2, k4, VB).

Conclusion: The results demonstrate, that a full kinetic analysis of the ^{18}F-FDG kinetics in NSCLC and metastatic colorectal cancer is helpful for the classification into short or long survival and may be used to identify those patients who may benefit from this palliative chemotherapeutic protocol. Furthermore, even an individual prognosis of survival can be achieved using kinetic FDG parameters of the first and third study in patients with metastatic colorectal cancer.

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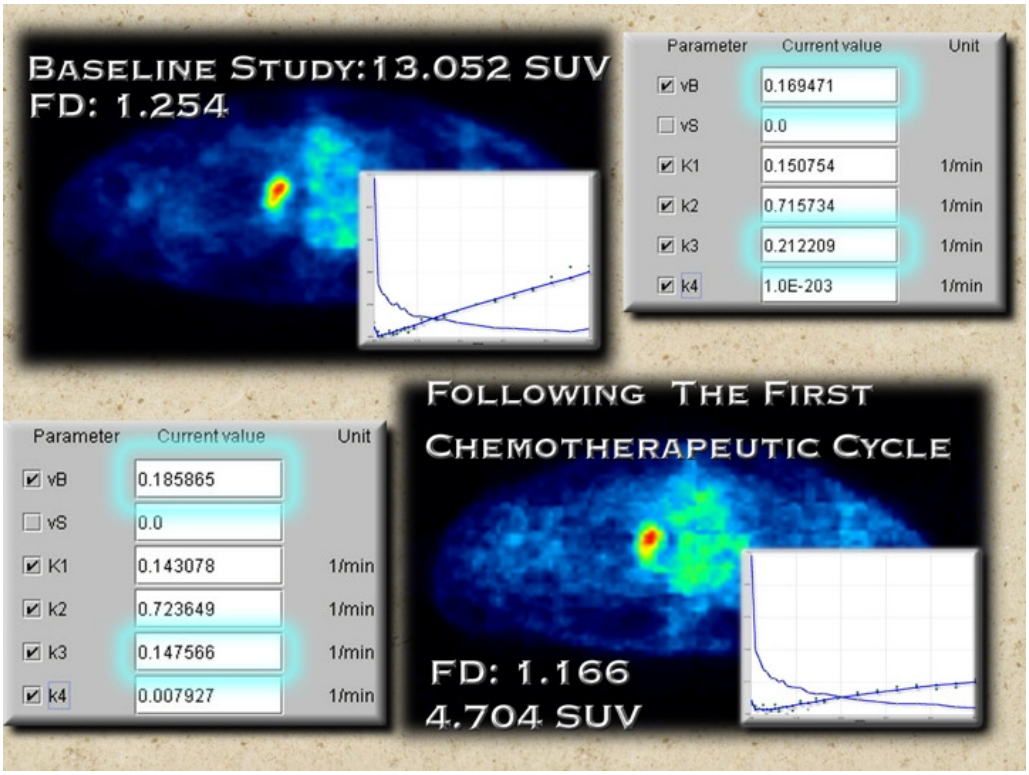

FIG. 1. FDG study prior and after one FOLFOX cycle in a patient with a lung metastasis of colorectal cancer located in the right hilar region. The kinetic data demonstrate a decrease in the phosphorylation rate k3 and a slight increase in the vessel density. This patient responded to FOLFOX chemotherapy and showed an overall survival of 801 days.

Importance of SPECT imaging in the assessment of tumour viability: Evaluation of an indegenous preparation of ^{99m}Tc-glucarate*

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Background: For developing countries SPECT systems continue to play an important role in the management of oncology patients. There is a pressing need for a suitable SPECT radiotracer for assessing tumor viability. An agent which is technetium based, clinically proven and inexpensive could serve millions of cancer patients especially in developing countries where facilities for positron emission tomography (PET) are not available. 99mTc Glucarate being a glucose analogue appears to be a suitable tracer for this purpose. However due lack of commercial interest it has not undergone formal clinical trials. Labelled with technetium pertechnetate (99mTcO4) this has been used as a tumour imaging agent in experimental studies. We report here the clinical evaluation of this tracer and importance of SPECT studies in lung and head & neck malignancies in this prospective study.

Method: This study comprises of two aspects and is a part of an ongoing multicentre IAEA co-ordinated research project. The indigenously produced glucarate kit containing glucarate (monopotassium) (12mg), sodium bicarbonate (16.8mg), acetic acid 0.1M (40 micro lt.), stannous chloride (0.1mg) and ascorbic acid (1mg), was prepared in the Radiochemistry Department Universidad de la Republica Montevideo, Uruguay. IAEA operational guidance on hospital radiopharmacy (operation level 3a) was followed and kit was approved after necessary analytical and animal studies. Labelling was performed by adding 99mTcO4 and incubating for 20 min. at room temperature. Radiochemical purity was more than 90% (chromatographic method). 25 patients enrolled till date. 15 patients had suspected lung carcinoma (14 male & 1 female with mean age 62 years) and 10 patients had suspected head & neck carcinoma (8 male & 2 female with mean age 53 years). All patients had a measurable lesion in CT scan and underwent biopsy. Post-treatment evaluation was performed in 4 patients. Consent for this procedure was obtained. 20 mCi of 99mTc glucarate was injected intravenously. Whole body images and SPECT of the area of interest was performed 4-5 hrs. post injection. SPECT imaging was performed with a dual head gamma camera 64x64 matrix (lung cancer), 128x128 matrix (head and neck malignancies), step and shoot acquisition and 25 sec/frame. Avid abnormal radiotracer concentration in the target lesion was considered positive for interpetation.

Results: In the initial phase of clinical trial 30 studies have been performed so far in 25 patients. 14/15 and 8/10 patients showed avid concentration of the radiopharmaceutical in the primary lesions in lung and head neck region respectively. The target to background ratio, delineation and localisation of the lesion was far superior and comparable to morphological imaging in SPECT images. Histology confirmed malignancy in 15 and 10 in the respective groups. Post treatment evaluation in 4 patients (5 studies) of lung carcinoma showed partial response (PR) in 3 and complete response (CR) in 1. Persistent glucarate concentration was seen and quantifiable in the PR group. No appreciable tracer concentration was seen in CR.

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Discussion: ^{99m}Tc-Glucarate is still an investigational radiopharmaceutical which has been initially used primarily in the early detection of myocardial infarction [1]. At the same time it was also found to accumulate in some tumours as well. However most of the few available studies in literature are on experimental animals. It has been seen to concentrate avidly in cell lines and strains in vitro and in murine tumours in-vivo. Accumulation was enhanced under hypoxic conditions in 12 of the 16 human and murine cell lines and strains studied and inhibited in the presence of nitroimidazoles [2]. ^{99m}Tc-Glucarate has also been shown to concentrate in human breast tumours (unpublished data). In xenografted BT20 breast tumours this has been found to have higher tumour uptake than ^{99m}Tc-sestamibi (MIBI) and can potentially localise drug resistant breast tumours [3]. However an ideal tumour imaging radiopharmaceutical should not only be helpful in detecting tumour but more importantly it should be able to assess the therapeutic response functionally but also be helpful in prognostication. A baseline study is required to assess the tumour avidity of the radiopharmaceutical. We have been able to achieve good tumour concentration of ^{99m}Tc-Glucarate and the findings so far indicate that it could be used to assess therapeutic response as well.

Conclusion: ^{99m}Tc-Glucarate is an easy to prepare radiopharmaceutical showing avid tumour concentration in lung and head neck malignancies. The results obtained so far suggests that ^{99m}Tc-glucarate is a potential tumour imaging agent with high sensitivity. The sensitivity was more with SPECT images providing better clarity, more confidence in interpretation and better comparison with morphological imaging This can be used for detection as well as assessing therapeutic response in malignancy. Clinical trial involving larger number of patients and potential comparison with FDG PET is underway.

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CME – BASIC PET

How FDG works: Basic skills in image interpretation

P. Conti

Image interpretation oncology

H.A. Macapinlac

CME – RADIOPHARMACY

Comparison of national PET radiopharmaceutical regulations

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In the United States (US), the European Union (EU) and Japan, physicians frequently prescribe formulations of drugs for patient care which are not available commercially, and require compounding. In the practice of Nuclear Medicine, Positron Emission Tomography (PET) presents a unique compounding challenge in the production of PET radiopharmaceuticals (RaPh), due to the short radionuclide half-lives [F-18 (110 minutes), C-11 (20 minutes), N-13 (10 minutes) and O-15 (2 minutes)], and the need to maintain high quality standards for human use "drugs", particularly intravenous formulations. As PET has progressed and the utilization of PET increases each country is developing regulations to manage cyclotron radionuclide production, compounding and quality control (QC).

Production of PET radionuclides in the US is currently regulated by the Nuclear Regulatory Commission (NRC). These radionuclides are then synthetically incorporated into the final PET RaPh for subsequent patient administration. Since these "drugs" are usually administered intravenously, the regulations for sterile compounding, or manufacturing, come under Pharmacy Practice, which for the US is the Food and Drug Administration (FDA). On receipt of a physician's order for a PET drug, pharmacists (or chemists) working under the authority and supervision of a physician, or a pharmacist working in a centralized PET Nuclear Pharmacy (licensed by an individual State), can compound the PET drug and dispense it for the patient.

In 2005, the US FDA published a proposed rule in the Federal Register on Current Good Manufacturing Practice (CGMP) for PET Drug Products [1]. These regulations are intended to ensure that PET drugs meet the requirements of the FDA Modernization Act (FDAMA) regarding safety, identity, strength, quality, and purity. These regulations will be included in the Code of Federal Regulation. After the rule is published, each site will have 2 years to comply with the new regulations, and to file a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) if product equivalency can be met. This will be a more stringent process as all PET drugs will be required to have an NDA.

Until the rule is finalized, the FDA has directed the PET community to produce PET drugs following the United States Pharmacopeia (USP) Chapter 823 [2] which sets guidelines for production and quality control testing, and lists the specific USP radiopharmaceutical monographs. PET drugs must be prepared according to a formalized Standard Operating Procedure, and the chemistry must be validated through 3 consecutive test runs performing defined QC procedures for pH, radionuclide identity, radiochemical and chemical purity, residual solvents, bacterial endotoxin (BET) and sterility. The specific activity must be such that the administered mass of the drug does not cause a detectable pharmacological response. The work area used for sterile operations should have a rating of Class 100, located in a controlled area with limited traffic.

The European Union (EU) Commission has also established GMP guidelines for production of RaPh included in the EudraLex (The Rules Governing Medicinal Products in the European Union) Volume 4, (EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use), Draft Annex 3 (Manufacture of RaPh). [3] The comments on Draft Annex 3 were due by March 30 2007. Currently, there is little difference between regulations for pharmaceuticals and those applied to PET. PET drugs must be manufactured in controlled areas. Access to controlled production areas require entrance through a gowning area and is restricted to authorized personnel. In case of use of closed and automated systems, "hot-cells" are usually suitable with a high degree of air cleanliness.

Quality control for short-lived RaPh may be carried out in two stages, before and after full analytical testing required in the appropriate EU Pharmacopeia Drug Monographs [4].

In Japan there is a “Standard of Compounds Labeled with Positron Nuclides Approved as Established Techniques for Medical Use, 2001 Revision” written by the Subcommittee on Medical Application of Cyclotron-Produced Radionuclides [5]. These are guidelines for PET RaPh produced in medical institutes for diagnosis. These Guidelines have been prepared by the Japanese Society of Nuclear Medicine, Committee on PET Nuclear Medicine, and the Japan Radioisotope Association and Medical Science and Pharmaceutical Committees. The manufacturing environment is outlined, and the area where the FDG is produced must be of high cleanliness, but the air-quality is not defined by Class. The synthesis of the FDG using a closed system mandates use of a hot cell having>Class 10,000 air quality. Operations requiring aseptic manipulation with open systems (such as preparation of reagents) should be carried out in an environment of > Class 100. Any Automatic synthesis (currently only FDG) apparatus used must be approved by Japanese Pharmaceutical Law. There are Standards for PET RaPh including F-18 FDG and O-15 labeled Oxygen, Carbon Monoxide and Carbon Dioxide gases. The QC tests required are essentially the same as US specifications.

In the future, as the PET field continues to expand, we will need to monitor international efforts and share experiences to improve radionuclide production, RaPh compounding processes and QC procedures.

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Quality Assuarance/Quality Control of PET radiopharmaceuticals

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Radiopharmaceuticals for positron emission tomogoraphy (PET-RP) are defined as RPs which is (1) used for PET diagnosis but not therapy, (2) produced at on-site cyclotron facility, (3) labeled with radionuclides and (4) ultra-shortlived. From these unique characteristics, special consideration is required for quality assuarance (QA)/ quality control (QC) as follows:

(1) toxicity is not a problem for main constituent (radiolabeled compound), but contaminants;

(2) appropriate lead shielding, and quick/remote handling is required; and

(3) daily preparation and quality check before use is essential.

In PET facility, PET-RPs should be produced in daily basis under accurate QA/QC. In this lecture, concept and actual manipulation for QA/QC will be discussed using F-18-2-fluoro-2-deoxy-D-glucose (FDG) as a typical example in PET facility.

QA/QC requires accurate maintenace, opreration and traceable record for them. To assure them, detailed manuals and record forms should be prepared. Traceable records include maintenance logs and operation logs of all the instruments for production and analysis, and production logs and quality logs for each RPs. Each logs should be signed by an operator(s) and countersigned by an inspector(s).

To confirm the quality of each RP, radionuclide purity, radiochemical purity, chemical purity, osmorality, acidity(pH), pyrogenicity, sterility, and so on, should be checked before use, although sterility is confirmed later because it requires a couple of days. To perform the quality check in a short period safely and cost-effectively, simple but reliable methodologies should be selected. For radionuclide purity, multi-channel analyzer with Ge-detector is ideal but measurelent of half-life is commonly used. For chemical analysis, thin-layer chromatography and/or high-performance liquid chromatography with UV detector and radioactivity detector are used. Acidity (pH) can be measured with pH meter but test paper is considered to be useful for routine practice. Pyrogenicity is checked by Endotoxin analyzer.

There are several commercially available systems for QC. These systems automatically perform the QC analysis and print-out the results. However such a system also requires complecated maintenance and QC of the system itself.

In this presentation, various practical issues for QC/QA will be listed and examples will be presented.

CME – IMAGE INTERPRETATION

NEUROLOGY & CARDIOLOGY

Single-photon emission computer tomography (SPECT) and positron emission tomography (PET) imaging in cardiology

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Nuclear imaging procedures are well-established diagnostic tools in clinical cardiology, providing noninvasive information about myocardial perfusion, cardiac function and metabolism. Scintigraphic parameters provide relevant information that aids in everyday clinical decision making for referring physicians.

During the past two decades the clinical role of nuclear medicine procedures in cardiology has evolved significantly. At the beginning, the diagnostic role of nuclear medicine in detecting myocardial ischemia in patients with suspected coronary artery disease has been emphasized and myocardial perfusion imaging with exercise or pharmacological stress testing is a widely accepted technique for the detection and localization of coronary artery disease. The development of Tc-99m labeled perfusion tracers permits combined myocardial perfusion and left ventricular (LV) function studies at a single testing interval. Thus, the potential advantages of simultaneous assessment of myocardial perfusion ad LV function have been recently outlined. Gated imaging of the perfused myocardium is a well-established technique for this purpose, with a single injection of a Tc-99m labeled perfusion tracer. Recent data have demonstrated the impact and clinical role of these studies in the diagnosis of patients with suspected or known coronary artery disease. The addition of functional information to perfusion data has shown to improve the detection of multi-vessel disease.

Subsequently, cardiac radionuclide imaging has made significant advances in the determination of prognosis in patients with ischemic heart disease, preoperative risk assessment for patients undergoing non-cardiac surgery and assessment of the efficacy of revascularization in patients undergoing coronary artery bypass surgery or interventional procedures. A key role of myocardial perfusion imaging has been its ability to provide prognostic information in patients after acute myocardial infarction, in patients with chronic coronary artery disease and in patients scheduled for major surgery.

The use of exercise or pharmacological myocardial perfusion imaging in the assessment of interventions in chronic ischemic heart disease is indicated for the evaluation of restenosis after percutaneous transluminal coronary angioplasty (PTCA) in symptomatic patients, in the assessment of ischemia in symptomatic patients after coronary artery bypass grafting (CABG). Radionuclide techniques are also indicated in the assessment of selected asymptomatic patients after PTCA or CABG, such as patients with an abnormal electrocardiographic response to exercise or those with rest electrocardiographic changes precluding identification of ischemia during exercise. SPECT exercise imaging is an excellent tool for the detection of restenosis and disease progression after PTCA in the settings of one and multi-vessel angioplasty and complete and partial revascularization. In addition, myocardial imaging studies offer several advantages over stress electrocardiography, particularly in patients with abnormalities of the resting electrocardiogram, multi-vessel coronary disease, or a limitation to exercise stress testing. Exercise scintigraphy after CABG demonstrates improved regional myocardial perfusion in most patients. After CABG, the New York Heart Association's functional class improved significantly. Early (less than 3 month) post-CABG myocardial imaging may be useful for the detection of peri-operative infarction or if early graft closure with recurrence of angina symptoms is suspected. Beyond 3 months, and following the recovery of hibernation effects, noninvasive cardiac imaging is useful to detect asymptomatic graft attrition and the recurrence of myocardial ischemia.

More recently, particularly attention has been focused on the ability of nuclear cardiology to characterize myocardial tissue and to assess myocardial viability in patients with ischemic LV dysfunction. In patients with coronary artery disease, the presence of myocardial necrosis, post-ischemic stunning and hibernation can determine left ventricular dysfunction leading to ischemic heart failure. The prognosis of these patients is still poor and the long-term results of medical management remain discouraging. It is now well established that ventricular dysfunction is often a reversible process and ventricular function may improve following myocardial revascularization. Patients with extensive areas of hibernation treated medically have a worse prognosis as compared to those who undergo revascularization with a similar extent of viable myocardium. Therefore, an accurate non-invasive assessment of myocardial viability with the preoperative differentiation between hibernation and stunning and irreversibly necrotic tissue is important for clinical decision-making to select patient candidates for revascularization. Radionuclide imaging techniques evaluating myocardial perfusion, cell membrane integrity, ventricular function and cardiac metabolism have demonstrated clinical utility in the assessment of myocardial viability and in predicting improvement of ventricular function and prognosis after coronary revascularization.

Image interpretation: Neurology (SPECT and PET)

S. Minoshima

CME – THERAPY ASSESSMENT AND PLANNING

Therapy assessment & planning in lung cancer

H.A. Macapinlac

Essentials of PET/CT computation and QA for treatment planning/follow-up

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FDG-PET/CT is increasingly used for the diagnosis and staging of malignant disease. However, a further strength of this imaging modality is the ability to assist in both planning and monitoring therapy, thereby improving the overall efficacy of the treatment, once diagnosis and staging have been established. For radiation therapy, treatment plans have traditionally been based primarily on anatomical images from CT or, more recently, MR. High resolution, three-dimensional anatomical images of the tumor and associated environment are used to devise a radiation treatment plan that maximizes dose delivery to malignant tissues and minimizes toxicity due to irradiation of surrounding structures. However, even before the appearance of PET/CT, it was recognized that FDG uptake is a better indicator of malignant tissue than anatomical density changes. Given the documented sensitivity of FDG-PET to detect malignancy, the gross tumor volume (GTV) can, in principle, be delineated with greater accuracy based on PET and CT images than on CT images alone. Prior to PET/CT, image fusion was performed using software with a success rate strongly influenced by inherent alignment errors arising from patient positioning differences. Now, however, with PET/CT, accurately aligned PET and CT images are routinely available for treatment planning, images that are acquired within a few minutes of each other reflecting a consistent anatomical and functional assessment of the disease. Since PET offers the possibility of imaging various aspects of tumor biology such as glucose utilization, proliferation, hypoxia and angiogenesis, an IMRT plan can be developed on an individual basis that delineates and treats a biological target volume (BTV) reflecting a particular metabolic pathway.

There is a growing body of literature documenting the changes in treatment plans resulting from the incorporation of the molecular (PET) signal. For lung cancer in particular, where the CT images can be particularly misleading due to the presence of atelectasis and other non-malignant processes, changes in planning target volumes (PTV) of 30-80% have been reported. These changes include both an increase in volume due to the identification of additional locoregional disease or distant metastases unsuspected from the CT scan, and a decrease due to the mismatch between active tumor and the corresponding anatomical abnormality seen on CT. Significant PTV changes are also found for brain tumors and in head and neck cancer. Indeed, a recent study demonstrated closer agreement between the GTV from the PET images and the corresponding surgical specimen than between the specimen and the GTV defined from the CT or MR images. For the patient, the effect on outcome and survival is more significant than a change in treatment volume. A recent study found that for patients with brain tumors, the incorporation of the molecular signal into the treatment plan resulted in an 80% increase in survival time, from 5 to 9 months.

While the definition of an accurate image-based BTV is obviously an advantage for treatment planning, it is by no means straightforward. The accurate delineation of the BTV is dependent on the definition of a suitable image threshold distinguishing malignant from benign or necrotic cells. The appropriate threshold will depend on the particular biological process being imaged and may be more difficult to establish for non-specific biomarkers such as FDG that is taken up by all cells using glucose. Typical thresholds are expressed as a percentage of the maximum uptake value (SUV_{max}) in the tumor and are usually in the range of 40-50% of SUV_{max}. Voxels with values exceeding this threshold are considered to be malignant thus allowing the boundary of the tumor to be delineated.

Another important role for molecular imaging and PET/CT is in assessing treatment response and follow-up. Traditionally, response has been based on anatomical changes as defined by the RECIST criteria. It is now recognized that there can be a functional response to therapy without necessarily incurring a corresponding morphological change. Indeed, the functional change may be an earlier and more sensitive indicator of response. Recent publications suggest that, for chemotherapy, response as early as three weeks after the start of treatment can be assessed by changes in FDG uptake: decreasing uptake is suggestive of response. For radiation therapy, the situation may be more complex due to local radiation damage that causes an initial increase in FDG uptake followed by a decrease as the number of viable tumor cells declines. Early assessment of response may therefore be more problematic for radiation therapy.

This presentation will summarize the role of PET/CT in planning radiation treatment and assessing response both during treatment and for follow-up. The focus will be on the integration of PET/CT into treatment planning and the challenges of computing the BTV based on the molecular image. The potential use and availability of different biomarkers will also be mentioned briefly.

POSTER SESSION I

CLINICAL PET

^{18}F-FDG PET/CT in the evaluation of transitional cell carcinoma of the upper urinary tract

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Background: Transitional cell carcinoma (TCC) accounts for up to 10% of the upper urinary tract neoplasms. Like in other type of tumors, preoperative staging is essential for an adequate treatment selection. In the management of TCC lymph nodes involvement and distant metastases detection are critical to decide either between radical surgery or chemotherapy. Metastases occur to the lungs, liver and bone, with direct extension into the retroperitoneum. Due to the frequent multicentric presentation of TCCs, of both synchronous and metachronous natures (bilateral in 2 – 10%), a close follow-up of patients is also important. Traditional imaging modalities, such as intravenous or retrograde pyelography, ultrasonography, CT, and/or MRI used to rule out nodal spread or to assess distant metastases have limited accuracy in TCC. CT and MRI use the size of lymph nodes of more than 1 cm as the main criteria for malignancy. Since ^{18}FDG PET/CT is based both in metabolic changes (PET) and anatomical abnormalities (CT) the multimodality fusion images have demonstrated higher accuracy than each technique by separated in cancer diagnostic. However, the renal excretion of ^{18}FDG has limited its use in urological malignancies. Nevertheless, this technique is considered a valuable tool for lymph nodes and distant metastases detection. There are very few reports in the medical literature dealing with ^{18}FDG PET/CT results in patients with TCC, most of them are disappointing mainly due to its focus in the evaluation of the primary lesion instead of the spread of the disease. In this report we present our initial experience in the evaluation of patients with TCC with ^{18}FDG PET/CT.

Methods: We studied retrospectively a total of 11 patients (6 males and 5 females); mean age 64.4 years (range 47 – 80) with histologically proven TCC of the upper tract. Two patients were studied for initial pre-surgical staging. The remaining were evaluated for post-surgical re-staging. Surgical procedure was done 2 to 12 months prior to the exam in 7/9 patients and two to four years before in 2/9. All the PET/CT scanners were acquired in a Siemens Biograph 6 Hi-Rez system. PET images start approximately 50 minutes after the injection of 10 mCi (370 MBq) of ^{18}FDG associated to a full diagnostic CT with IV contrast media injection. Patients were fasting and with glucose plasma level <140 mg/dL. The “maximum standard uptake value” (SUV Max) was calculated in all hypermetabolic lesions. All the studies were read simultaneously by both qualified nuclear medicine physicians and radiologists. Based on the “fusioned” ^{18}FDG PET/CT results, patients went to surgery, chemotherapy or follow-up.

Results: Among the 11 patients, 6 (54.5%) presented abnormal PET/CT findings. Five of them had multiples lesions, mostly hypermetabolic pulmonary nodules and distant lymph nodules, including cervical and supraclavicular involvement. The average SUV Max of the lesions was 6.6 g/mL, (range 2.5–19.8 g/mL), and the size ranged between 6 ad 54 mm. All of these patients have histopathological examination demonstrating metastases either by surgical exploration or percutaneous needle biopsy. In the two patients referred for pre-surgical staging, the primary tumor was seen in the CT, but ^{18}FDG metabolic activity was not easily assessed because of the normal activity in urine. Nevertheless, in both of them hypermetabolic distant metastases were found, changing the clinical management. In 5 patients neither hypermetabolic lesions nor CT abnormalities were found. In this last group no evidence of recurrences have been demonstrated after 4 to 13 month of clinical and complementary imaging follow up. Using the multimodality criteria (PET/CT) no false positive or false negative results were found in this series.

Conclusions: Our initial experience shows an unexpected avidity of ^{18}FDG in TCC metastases, validated by significant high SUV's, even in milimetric lesions. Even though the small number of patients in this study does not allow us to make any solid conclusions regarding to accuracy of this imaging modality, our results suggest that ^{18}FDG PET/CT might be a promising technique for the initial pre-surgical staging and subsequent follow up of TCC patients. Regarding the evaluation of the primary lesions, our findings are similar to those described in the medical literature: the renal excretion of ^{18}FDG masks the visualization of the tumors in the urinary tract. Due to the lack of urinary excretion of ^{18}F-choline or ^{11}C-choline, these radiopharmaceuticals should be the agents of choice to detect both the primary tumor and metastasis of TCC. Extended trials with more patients and longer follow up periods are needed to precise the role of ^{18}FDG PET/CT in the study of TCC.

^{18}F-FDG PET/CT in the evaluation of gallbladder carcinoma - Initial experience

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Background: Gallbladder carcinoma, beside gastric and breast cancer, is one of the leading cause of death for cancer in Chilean women reaching a mortality rate of 12.9 per 100.000 women. The global prognosis remains poor, with global lethality around 95%.

The most frequent clinical manifestations are: incidental finding in a biopsy of a laparoscopic cholecystectomy, gallbladder mass with or without jaundice and peritoneal carcinomatosis. Usually the diagnosis is too late, most patients show invasion of nearly organs and lymph nodes involvement.

Like in other type of tumors, preoperative staging is essential for an adequate treatment selection. Treatment of early stage or locoregional involvement is surgery and chemo-radiotherapy. In advances stage only palliative chemotherapy or palliative cares are indicated.

In local disease, imaging tests are useful for detecting lymph nodes, hilar or hepatic involvement, and to rule out spread metastases. Conventional imaging modalities, such as ultrasonography, CT, and MRI may underestimate disease extension.

There are few experience of ^{18}FDG PET-CT and gallbladder carcinoma communicated in the medical literature. Most of these publications are dealing with differential diagnosis of gallbladder tumors for detection of malignancy. In this report we present our initial experience evaluating patients suffering from gallbladder carcinoma with ^{18}FDG PET/CT. The goal of this study was to assess the metabolic activity, localization and extension of gallbladder tumor by PET/CT.

Methods: We studied prospectively 17 consecutive patients (2 males and 15 females); mean age 56.6 years (range 33 – 77) with histologically proven gallbladder carcinoma. Eleven patients were studied after cholecystectomy. The remaining were unresectable at the time of diagnosis. Clinical indications for ^{18}FDG PET-CT were: to evaluate surgery chance in 8 patients, chemotherapy response in 2, staging and follow up in 3 and to confirm disseminated disease seen in previous CT in 4. All PET/CT studies were acquired in a Siemens Biograph 6 Hi-Rez system. PET images start approximately 50 minutes after the injection of 10 mCi (370 MBq) of ^{18}FDG associated to a full diagnostic CT with IV contrast media injection. Patients were fasting and with glucose plasma level <140 mg/dL. The "maximum standard uptake value" (SUV Max) was calculated in all hypermetabolic lesions. All the studies were read simultaneously by both qualified nuclear medicine physicians and radiologists.

Results: Among the 17 patients, 13 showed abnormal PET/CT findings demonstrating multiple hypermetabolic foci, 12 of them considered as advance stage. SUVmax in the gallbladder varied 3.2 to 8.5 g/ml. Hypermetabolism in the liver was detected in 9, in the hepatic hilium in 9, porto-caval region in 7, retroperitoneal lymph nodes involvement in 5, peritoneal carcinomatosis in 3 and other localizations in 7. There was one false positive study in one patient with an internal mammary lymph node involvement corresponding to mycobacterium tuberculosis and also in one inflammatory lymph node due a recent cholecystectomy in the same patient.

Four patients had negative ^{18}FDG PET/CT finding for metastasis. In 3 of them no relapse has been detected after 6, 7 and 12 months respectively of follow up. In the remaining patient surgery demonstrated hepatic and lymph node involvement due to a mucinous adenocarcinoma ("signet ring cells").

The final medical decision was palliative measures in 12 patients, surgery in 2 and follow up in 3 patients with negative ^{18}FDG PET/CT. ^{18}FDG PET/CT supported medical management, avoiding unnecessary radical surgery in 7 patients.

Conclusions: Our initial experience with this limited number of patients shows a high ^{18}FDG uptake in gallbladder carcinoma. PET was also useful for detecting residual gallbladder carcinoma. Since ^{18}FDG PET/CT is based both in metabolic changes (PET) and anatomical abnormalities (CT) the multimodality fusion images allow higher accuracy to identified the precise localization of lymph node involvement what is crucial for an adequate staging of the disease. However, more experience is needed, mainly in early stages. Like in other oncologycal applications ^{18}FDG PET/CT must be interpreted with caution in patients with recent surgery and infection/inflammation diseases. In our series a false positive was observed in lymph nodes in one patient with recent cholecystectomy and tuberculosis. Additionally, one false negative study was found in a patient with a mucinous adenocarcinoma (signet ring cells) which is recognized as a tumor with low ^{18}FDG uptake due to the high content of mucine.

Our preliminary results suggest that ^{18}FDG PET/CT might be a promising technique for the initial pre-surgical staging, helping medical decision in this kind of cancer. Extended trials with more patients and longer follow up periods are needed to precise the role of ^{18}FDG PET/CT in staging and follow up of patients with gallbladder carcinoma.

Usefulness of FDG–PET in the evaluation of patients with colon and rectal cancer in a PET center in Chile

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Introduction: FDG PET is a useful imaging technique in the management of patients with gastrointestinal tumours, mainly in oesophageal and colorectal cancer. In Chile, colorectal cancer is a prevalent disease, representing the 7th cause of death in men and 6th in women. The aim of the study was to assess FDG-PET value in the management of colorectal cancer in the first PET center in Chile.

Material and Metods:
Population: In a retrospective analysis, we studied 130 patients with 159 PET scans, 56% corresponded to women.

Group A rectal cancer: 42 patients (55 studies), mean age 61 ± 11 y.o. (range 39-80)

Group B colon cancer: 88 patients (104 studies), mean age 61 ± 11 y.o. (range 39-80).

Referral: In the whole population, 53% were studied by recurrence suspicion (31% with increased CEA levels with negative anatomical imaging), 33% for restaging, 8% for therapy control and 6% for staging. Eighty-five % was submitted to surgery (range: 1m -7y) and 42% presented local or distance dissemination; 70% have received chemotherapy and 23% associated radiotherapy.

Technique: Whole-body images were acquired with a dedicated high resolution PET Siemens Ecat Exact HR+ camera 60 minutes after injection of intravenous F18-FDG, produced at the Chilean Nuclear Energy Commission (mean dose: 12 mCi). Visual analysis and semi-quantitative standardized uptake value (SUV) were performed by a consensus of 5 nuclear medicine physicians.

Results: 65% of the PET studies were positive, showing hypermetabolic tumoral uptake (63% studies in colon cancer and 69% in rectal cancer). In 30% from the positive cases liver lesions were found, 52% of them without other lesions. In 75% from positive studies there was extrahepatic involvement. In the group B, local recurrence was found in 37%. In 48% cases there was good correlation between anatomical images available and FDG and in 42% new unknown lesions were found with PET.

CEA levels: they were available in 62% of the cases (71% of them increased); the correlation with FDG was 77%; there were 10 cases with negative CEA and positive PET. CEA positive with FDG positive *Odds Ratio* corresponded to 7.58 [C.I: 2.8-20.3]. (Figure 1).

Follow-up: In 9 patients surgery was performed in sites with positive FDG, confirming all lesions (lung, liver and rectum). In 49 cases there was clinical follow-up:

A) 75% of those with positive PET received additional chemotherapy (4 patients deceased)

B) Good evolution with negative PET was seen in 79% (follow-up range: 3m – 3.5y); 2 patients presented elevated CEA levels without demonstrated lesions and 2 others showed metastases, at least 6 months after PET.

Conclusion: FDG - PET has great value in colorectal cancer evaluation, mainly in restaging and patients with suspected recurrence.

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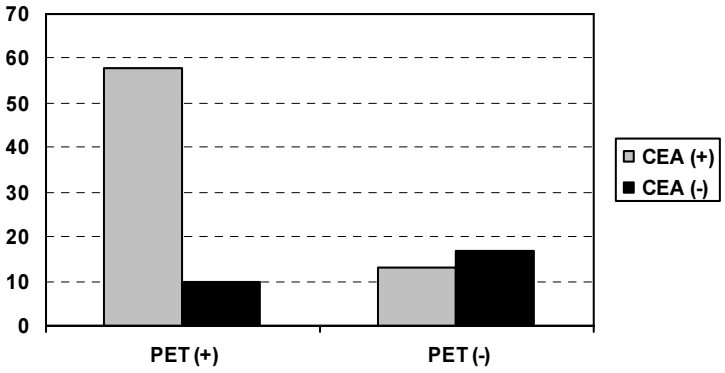

FIG. 1. Association between CEA and FDG-PET results.

Gastrointestinal stromal tumors (GIST) assessment using ^{18}F-fluor-deoxyglucose

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Introduction: Stromal gastrointestinal tumors (GIST) are relatively infrequent soft sarcomas, although correspond to the most common mesenchymal tumor in the gastrointestinal tract. Surgery is the main therapy during initial stages. Nearly a third of them could be malignant (higher risk) depending on the localization, size and histological parameters. Chemotherapy and radiotherapy have low therapeutic value. Specific molecular therapy associated to surgery using imatinib-mesylate (GLIVEC®) – a selective transductor signal inhibitor for some tyrosine-kinase receptors –is currently use. It is helpful in non-resecables, recurrent or metastatic tumors. Metabolic fluorine18-deoxyglucose (FDG) allows to characterize tumor behavior demonstrating good predictive value. Promising results have been obtained using adjuvant and neoadjuvant protocols. There are some multicenter in-course trials including FDG in order to evaluate early response to GLIVEC® therapy. Other recently developed molecules such as sunitinib malate (SUTENT®) are used in non-responders.

Method: We have performed 18 FDG studies to 15 GIST patients referred from different centers in a period of 48 months, corresponding approximately to 1% of all cancers in adults. and to 6% of gastrointestinal tumors. The mean age of the group was 57±10.6 y.o., ranging from 33-72 years, 60% of the patients were male. GIST primary localization corresponded to jejunum or ileum (4), duodenum (3), esophagus, stomach (1) besides, 2 retroperitoneal/extra intestinal cases and 5 disseminated cases with no clear origin site. Eight out of fifteen patients presented known dissemination when FDG was performed. PET-FDG was performed to assess: a) medical therapy control in 9 cases: 7 with GLIVEC®, 1 with SUTENT® post GLIVEC® and 1 post chemotherapy, b) restaging in 6 and c) staging in the other 3 cases (1 submitted to surgery and 1 extensive tumor to decide GLIVEC® therapy). All but one patients already had surgery performed with a mean 12±10m prior to their first FDG. GLIVEC® therapy ranged between 3-43 m. Mean FDG dose was 481±74 MBq injected with a mean serum glucose level of 89±9 mg/dl. Images were obtained with a dedicated PET system Siemens ECAT EXAT HR+. Quantitative analysis using SUV measurements were used for metabolic follow-up.

Results: 44% of FDG studies were positive for malignancy. Within the staging group, 2 recent post-surgery patients were negative and the disseminated non operated was positive. Concordance with recent anatomical or functional images [Computed Tomography (CT), bone scintigraphy, abdominal echography or prior FDG].was observed in 61% of the studies. New unknown lesions were found in 7 studies (39%) located in mediastinum, liver, peritoneum and skeleton. Only 3/8 cases with molecular therapy had negative FDG for active tumor; other 2 cases presenting 20% and 50% of CT regression had clearly positive FDGs without new lesions. Three patients had FDG follow-up: one remained negative, other progressed with new lesions and the non-operated case with extensive dissemination presented total FDG regression (Figure 1).

Conclusion: In our initial experience, functional images with PET-FDG demonstrated great value for metabolic control of molecular therapy, staging and restaging post surgery of GIST tumors.

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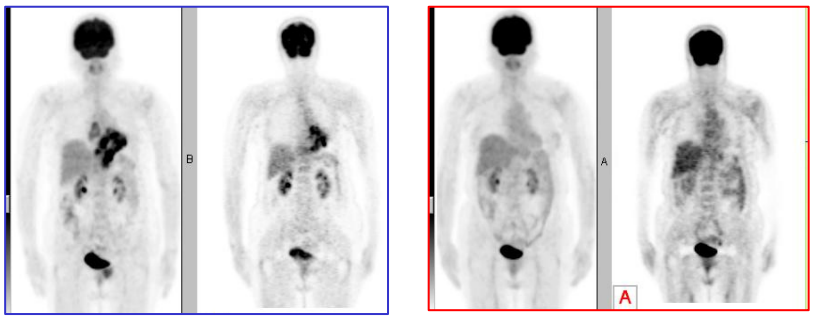

FIG. 1. Basal FDG (left): Hypermetabolic mass in posterior toraco-abdominal region concordant with malignant tumoral activity (SUV_{max}:24) as well as in two sites in skeleton. FDG control (right) performed 3 months later using GLIVEC® demonstrated: total lesions regression.

The value of 18F-FDG PET imaging in the differential diagnosis of Parkinsonian disorders using statistical parametric mapping method

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Aim/Background: Parkinson Disease (PD) and Alzheimer Disease (AD) are the most common neurodegenerative disorders. There are overlaps in clinical characteristics between PD and AD. [1] Preliminarily evaluating the value of FDG-PET imaging in the differential diagnosis of Parkinsonian disorders such as Idiopathic Parkinson's disease (IPD), progressive supranuclear palsy (PSP), cortico-basal ganglionic degeneration (CBGD) and multiple system atrophy (MSA).

Methods and materials: 10 patients with Parkinsonism: 7 patients (mean age 68.0 ± 6.07 years; M/F: 6/1) with IPD, 1 patient (56 years; Female) with MSA, 1 patient (56 years; Male) with CBGD and 1 patient (70 years; Male) with PSP and 36 normal controls, who matched in age, sex and years of education, were enrolled in our study. To assess the relative cerebral glucose metabolic rate (rCMRglc), FDG-PET imaging was performed in all subjects. The individual IPD, MSA, CBGD and PSP patients were compared with a normal control group using a two sample t-test of SPM (uncorrected $P<0.001$, extent threshold =100 voxel).

Results: As compared with the normal controls, The IPD patients showed significant hypometabolism in bilateral parietal and occipital association areas and prefrontal cortex, however, the glucose metabolism was increased in the putamen and globus. The MSA patient showed significant hypometabolism in bilateral lentiform nuclei compared to the normal controls. The CBGD patients showed hypometabolism in the unilateral cortical areas such as left frontal cortex and in the basal ganglia such as unilateral caudate and thalamus contralateral to the affected side compared to the normal controls. In addition, PSP patient showed significant hypometabolism in the thalamus, midbrain and the middle frontal gyrus compared to the normal controls.

Discussions: The regional cerebral glucose metabolism was found to be different between PD and PDD degenerative patients. [2] The AD-associated PET pattern typically presents as focal cortical hypometabolism in bilateral parietal, temporal and/or frontal lobes, however these changes can also be seen in PDD and DLB. Greater hypometabolism was observed in parietal-temporal association cortex in AD group as compared with PDD group. [3] The occipital hypometabolism can be used to differentiate the DLB group from AD and PDD groups.

Conclusions: Assessment of the 18F-FDG PET images using SPM-supported reading may be a useful adjunct to a clinical examination when making a differential diagnosis of Parkinsonism.

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The clinical value of the qualitative and semiquantitative ^{18}F-FDG PET/CT in the detection of primary breast cancer and lymph node metastasis

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^{18}F-FDG PET/CT has been proven particularly helpful in oncology [1]. The purpose of this study was to assess the utility of the qualitative and semiquantitative analyses of ^{18}F-FDG PET/CT in the detection of primary breast cancer and lymph node metastasis.

27 female patients (age range 32-79 yrs, mean 56 yrs), who were highly suspected of breast cancer clinically, underwent breast FDG PET/CT imaging and mammography. Two analysis methods of FDG uptake were used to differentiate malignant lesions from benign. One was semiquantitative method by measuring the maximum standardized uptake value (SUV), using two thresholds (SUV_{lesion} >2.5, SUV_{lesion} > mean plus 2 SD of SUV_{normal}). The other was qualitative method according to the distribution of FDG in the lesions. If FDG uptake was distinctly focal and higher than liver activity, or though uptake was equal or lower than liver activity but higher than normal breast with malignant characteristics in CT imaging, the lesion was categorized as malignant.

32 breast lesions were found in operation and all were confirmed histologically. And 25 of 32 lesions were malignant and 7 benign. Qualitative assessment correctively diagnosed 19 of 25 breast carcinomas with sensitivity, specificity 76%, 85.7%, respectively. SUVs of malignant lesion, benign lesion and contralateral normal breast tissue were 5.08+/-3.55, 1.17+/-0.31, and 0.76 +/- 0.52, respectively. The SUV of malignant lesion was significantly higher than those of contralateral normal breast and benign lesion ($P<0.01$ all). There was no significant difference between benign lesion and normal breast in SUV ($P>0.05$). When using +2 SD of mean normal breast SUV as the cutoff value, the sensitivity and specificity of diagnosing breast malignant lesions were 96%, 28.6%, respectively. By using threshold of SUV 2.5, the sensitivity and specificity were 72%, 28.6%, respectively. 10 patients were proved to be with regional lymph node metastasis. Using threshold of SUV 2.5, the sensitivity and specificity were 60%, 92.3%, respectively. By qualitative analysis of PET/CT, the sensitivity and specificity of diagnosing lymph node metastasis were 60%, 84.6%, respectively.

The single-time-point SUV of 2.5 has been cited as the optimal threshold in pulmonary malignancies for diagnosing lung cancer [2]. However, this threshold may not be applicable to breast cancer, because the reported average SUV is lower in breast cancer cells as a result of less complete phosphorylation of ^{18}F-FDG [3]. In detecting primary breast carcinoma with FDG PET/CT, higher sensitivity could be acquired when using SUV>mean plus 2 SD of SUV_{normal} as the cutoff value for differentiating malignant from benign. The qualitative analysis was with higher specificity.

PET/CT imaging with the qualitative and quantitative analysis is a simple, noninvasive and effective method in assessing patients with primary breast cancer and lymph node metastasis.

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The study of the impact of breast density on 18F-FDG PET detectability of breast cancer: Comparison with mammography

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It has been reported that the breast density can affect the mammographic detectability of breast cancer [1]. And the breast density also affects the uptake of ^{18}F-FDG in normal breast tissue [2]. This study aimed to evaluate the impact of breast density on ^{18}F-FDG detectablility of breast cancer, compared with mammography.

25 female patients with breast cancer (age range 37-77 years, mean age 58 years) and 29 female subjects with normal breast tissue (age range 40-74 years, mean age 51 years) underwent both ^{18}F-FDG PET and mammography. All the patients with breast cancer were certified by pathology. The breasts were categorized as extremely dense, heterogeneously dense and primarily fatty according to the Breast Imaging Reporting and Data System (BI-RADS). The maximum standardized uptake value (SUVmax) of ^{18}F-FDG in different breast tissues were measured separately.

Mammography showed that 12 of 25 patients with breast cancer had heterogeneously dense breasts, 5 had extremely dense breasts, and 8 had primarily fatty breasts. And 15 of 29 subjects with normal breast tissue had heterogeneously dense breasts, 9 had extremely dense breasts, and 5 had primarily fatty breasts. In extremely dense, heterogeneously dense and primarily fatty breast tissue of patients with breast cancer, the SUVmax were 10.6+/-4.88, 4.7+/-1.82 and 3.57+/-1.62, respectively. And in the corresponding breasts of subjects with normal breast tissue, the SUVmax were 0.78 +/-0.19, 0.55+/-0.18 and 0.24+/-0.07, respectively. The SUVmax were significantly higher for extremely dense breasts than primarily fatty breasts for both breast cancer and normal breast tissue ($P< 0.01$). Mammography detects breast cancer with sensitivities of 40%(2/5), 91.6%(11/12), 100%(8/8) in patients with extremely dense, heterogeneously dense, primarily fatty, respectively. And the sensitivity of ^{18}F-FDG PET was 100%(5/5), 66.6%(8/12), and 75%(6/8), respectively, based on the diagnose criterion SUV 2.5 as a cutoff between malignant and benign lesions. And the specificity of mammography detecting breast cancer was 33.3%(3/9), 66.6%(6/15) and 100%(5/5), respectively. The specificity of ^{18}F-FDG PET was 100%(9/9), 66.6%(6/15) and 60%(3/5), respectively.

Our results found that mammography only detect 2 patients from 5 breast cancer patients with extremely dense breast. The results of previous studies suggest that breast density is one of the strongest predictor of the failure of mammographic screening to detect cancer, which is coincident with our results. For the extremely dense tissure, all 5 patients with breast cancer were detected by ^{18}F-FDG PET. As it is known, ^{18}F-FDG PET can be helpful in the diagnosis of primary breast cancer, especially in patients with dense breast tissue, significant fibrocystic changes, fibrosis after radiotherapy, and inconclusive results from MR imaging and other imaging modalities [3]. And for the primarily fatty tissure, all 8 patients with breast cancer were detected by mammography, while 6 were detected by ^{18}F-FDG PET.

In this study, we found that the breast density does not affect the ability of ^{18}F-FDG PET to discriminate malignant from benign lesions, although the uptake of ^{18}F-FDG is different in different density breasts. By compared with mammography, the detectability of ^{18}F-FDG PET is significantly superior to mammography in the extremely dense lesions.

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Experiences on improving diagnostic accuracy of FDG PET by characterizing, reducing, and avoiding the high-level physiological uptakes at abdomen and pelvic region

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Background: FDG PET has been extensively used in oncology. However, the physiological uptakes, especially those at abdomen and pelvic region, sometimes produce misleading signals. We conducted series of studies on characterizing, reducing, and avoiding the most common pitfalls caused by physiological uptake of gastrointestinal system, female reproductive system, and urinary system.

Methods and materials:
1. To improve detection of gastric malignancy, a modified PET protocol was studied. The patients were suggested to drink 300-500 ml of cow milk to distend the stomach right before the scanning (nearly 1 h after FDG injection). To investigate the influence of ingested milk to FDG distribution, forty-three patients underwent both empty- and distended-stomach PET studies (79 and 72 studies, respectively) in their serial follow-up of non-gastric malignancies (the intervals were 24±15 months). For identification of primary tumor of gastric cancer, twenty-four cases underwent distended-stomach PET studies were compared with other 17 cases with empty-stomach studies. In addition, 1500 patients who referred to our center for evaluation of diseases other than gastric malignancies also underwent distended-stomach PET studies.

2. To characterize high-level physiological uptakes of uterus and ovaries, we analyzed 247 female patients (288 studies) without documented uterine or ovarian diseases. The menstrual statuses and phases of the patients and related pelvic examinations with other modalities were inquired before each PET study.

3. Seventy patients with suspicious abdominal or pelvic lesions on routine whole-body studies underwent delayed imaging nearly 3 h after FDG injection. Before the delayed imaging, the patients were suggested to drink water, ingest food, urinate, and even empty the bowels to change the physiological status of gastrointestinal and urinary systems.

Results:
1. There was no significant influence of milk ingestion on ^{18}F-FDG distributions to the heart (P=0.16), mediastinum (P=0.50), and liver (P=0.49), while the ratios of intense and moderate uptake of stomach reduced from 38.0% and 59.5% to 0% and 11.1%, respectively. With the normal gastric wall distended, malignant lesions were observed with higher contrast and clearer outlines, and could be detected at early stage in small size (1.2 cm) with mild uptake (SUV 1.8). From 1500 patients without documented gastric disease, three cases were incidentally found with suspicious regional uptake at the stomach, and were later proved as early stage gastric malignancies by gastroscopy and surgery.

2. In the 116 patients (131 studies) with regular menstruation, the endometrial uptakes were observed in inverted cone shape, with two peaks of uptake at the early menstrual flow phase and mid-cycle, respectively. The ovarian uptake was more prominent in the mid-cycle, and the foci of uptake had an ovoidal shape and located at left and/or right side superior-posterior to bladder. From early menstrual flow phase to late secretory phase of the menstrual cycles, the probabilities of mild uptake in both endometrium and ovaries were 7%, 86%, 80%, 58%, 20%, 40%, 64%, and 59%, respectively. No intense uptake was observed in the 17 patients (19 studies) presenting remarkable irregular menstrual cycle, 112 patients (136 studies) in menopause, and 2 patients without menstruation yet.

3. For the patients with suspicious abdominal or pelvic lesions, thirty-three cases were proved as malignancies by pathologic diagnosis and/or clinical follow-ups, thirty-three cases were diagnosed as physiological uptake, and 4 cases were benign. In delayed imaging, 21 cases had lesions with increased SUVs for more than 10%, 17 (81%) of which were proved as malignancies; 27 cases had lesions with decreased SUVs for more than 10%, and 23/27 (85%) were not related to malignancy, most of which were regional bowel uptakes and urine retention. The 4 pseudo-positives were caused by physiological uptake of uterus or ovaries, and were correlated well with the menstrual cycles. The 3 pseudo-negatives were gastric cancer, and although their SUVs decreased in the delayed imaging by gastric distention with foods, the lesions were actually more prominent with higher contrast.

Discussions: Gastric cancer is one of the most common malignancies, especially in Asian population. However, FDG PET routinely performed under fasting status demonstrates limited value to its diagnosis because of the high-level physiological uptake of stomach. Gastric distention just before FDG PET scanning can benefit the early detection and accurate evaluation of primary tumor of gastric cancer.

Physiological uptake of uterus and ovaries can mimic pelvic malignancies on FDG PET. For female patients with regular menstrual cycle, PET studies at late menstrual flow phase and early proliferative phase showed the least probability of intense or moderate physiological uptake.

Delayed imaging, especially after changing physiological status by drinking, food ingestion, urination, and bowel movement, can help to exclude the physiological uptakes of gastrointestinal and urinary system.

Conclusions: The diagnostic accuracy of FDG PET at abdomen and pelvic region can be improved by good understanding of the physiological uptakes, intentionally changing the physiological status, and proper arrangment of PET scanning.

The combined use of ^{11}C-choline and ^{18}F-FDG PET in the diagnosis of brain tumor

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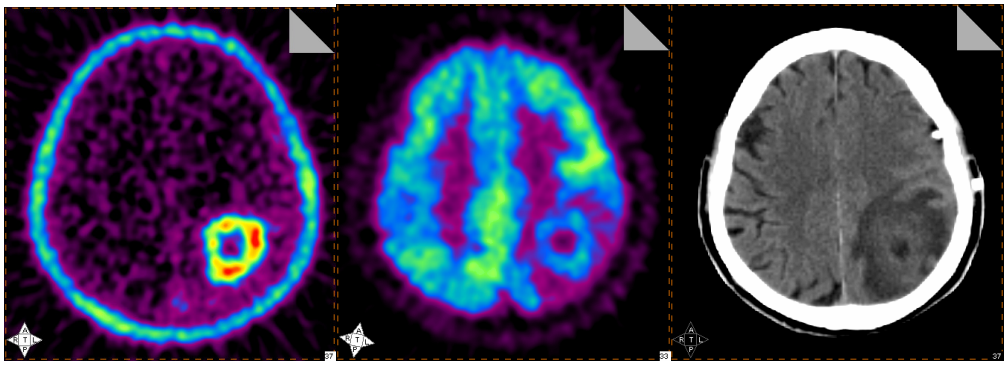
Object: Analyze the value of the combined use of ^{11}C-Choline and ^{18}F-FDG PET imaging in brain tumors.

Patients and Methods: 106 patients diagnosed or suspected with brain tumors between Mar 23rd 2005 and Feb 8th 2007 whom were confirmed by follow-ups. Both ^{18}F-FDG and ^{11}C-Choline PET imaging were performed on a Siemens Biograph Sensation 16 PET/CT scanner.

Result: In the 106 patients, 9 patients were misdiagnosed. Of all 9 misdiagnosed patients, 4 were false positive (1 abscess (Fig. 1), 1 tuberculosis, 1 benign gliocyte proliferation, 1 inflammatory pseudotumor) and 5 were false negative (3 metastases from lung cancer, 1 lymphoma, 1 glioma). Rate of false positive was 3.77%, rate of false negative was 4.72%, the accuracy of ^{11}C-Choline PET imaging was 84.9%.

Conclusion: ^{11}C-Choline PET imaging has certain ratio of false positive and false negative. The combination with MRI imaging, ^{18}F-FDG PET imaging and clinical information and improve the accuracy of diagnosis[1-2]. With proper application, ^{11}C-Choline is still one of the best choices for brain tumor PET imaging.



^{11}C-Choline PET ^{18}F-FDG PET MRI

FIG. 1. A 63-year-old male presented with right-sided weakness and decreased response for 10 days. MRI showed a mass in left parietal lobe. The Choline and FDG PET scan showed hypometabolism in the whole left parietal lobe except moderate uptakes forming a "ring" sign correlated to the enhanced foci on MRI images. The pathology was abscess.

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The value of F-18-FDG triple-head coincidence PET in the post treatment evaluation of patients with lymphoma

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The purpose of this study is to asses the prognostic value of FDG-PET performed with triple-head coincidence gamma camera during an early follow-up period and its accuracy in early detection of residual or recurrent disease in patients with Hodgkin´s disease (HD) and non-Hodgkin lymphoma (NHL).

The single centre study comprised 31 consecutive patients (median age 35 years; range 16-66 years) with primary or recurrent biopsy confirmed lymphoma which had follow-up of at least 12 months (median 20 months; range 12-39 months). PET studies were performed using IRIX hybrid PET camera with triple head coincidence imaging capability.

The long-term follow-up data after treatment and PET studies were extracted from the patients' medical files. Fifteen patients (5 NHL, 10 HD) were negative on PET scan. They did not receive any theraphy after FDG-PET, and no one relapsed in the follow-up. Twelve patients presented with clear FDG pathological accumulation in one or more sites previously shown to be involved by lymphoma. Ten patients received further therapy. Six of them never achieved complete remission (CR). Three patients entered CR but relapsed (5, 17, and 28 months after FDG-PET) despite of additional therapy. Two patients were noted as false-positive. In four patients only slightly increased FDG uptake was observed (equivocal findings).

This methodology was good enough for reliable prognosis in follow-up of our patients, especially in patients without FDG pathological fixation. False positive FDG uptake seems to be a problem. On the other hand, a negative PET scan is an important contribution in the management of these patients owing to its prognostic value, and can reassure patients and their doctors that disease is not active.

Dual tracer/dual isotope Ga-68 DOTA-NOC and F-18 FDG PET/CT – A one day protocol in a child with neuroblastoma for determining the receptor status and the metabolic tumor state

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We report on a 6-year-old boy with a history of neuroblastoma. The tumor was first diagnosed in March 2004, arising from the right adrenal gland as confirmed by fine needle aspiration biopsy, ultrasound, CT scan as well as tumor markers. Due to the size and extension, the tumor was inoperable at this time and two cycles of chemotherapy (vincristin, cisplatin, etopoxid and cyclophosphamid alterning with vincristin, carboplatin, etopoxid and cyclophosphamid) were given. Then, the patient underwent retroperitoneal surgery and the right adrenal gland and the tumor were completely resected. After the operation, the patient received 4 additional cycles of chemotherapy until March 2005. During August and September 2005 the patient complained about abdominal pain and recurrence was suspected. Ultrasound and CT scan were repeatedly performed, but were unclear. In December 2005, a I-131 MIBG scan (148 MBq, 4 mCi iv, planar images and SPECT from 24 hrs until 6 d p.i.) revealed only a normal left adrenal gland but no recurrence, proving that the tumor had no MIBG uptake.

In January 2006 the child (121 cm height, weight 21 kg) was submitted to the PET/CT Center of the Zentralklinic Bad Berka, Germany for receptor PET/CT using Ga-68/DOTA-NOC, a high affinity pansomatostatin analogue. NSE was determined in serum prior to the PET/CT study and was elevated (24.8 ng/ml, cutoff 15). The patient received 46 MBq (1.24 mC) Ga-68 DOTA-NOC i.v. and a whole-body PET/CT was performed 75 min. p.i.. There was no abnormal uptake proving that the recurrence had no somatostatin receptors.

After this negative result it was decided to perform additionally a F-18 FDG PET/CT study (with contrast enhanced low dose CT scan). After a fasting time of 6 hours, the patient received 151 MBq (4.1 mCi) F-18 FDG. Whole-body PET/CT was performed 75 min. p.i. and a recurrence was clearly depicted as hypermetabolic tumor (SUVmax. 8.1, molecular tumor volume (MTV) 15,2 cm^3, 27 x 27 x 40 mm in diameter, craniocaudal extension 4.5 cm) between the vena cava inferior and the aorta with extension to the psoas muscle and infiltration of the right renal artery. Additionally, a weak hypermetabolic focus was detected in the right spina iliaca anterior superior (SUV 2.0). The results of the F-18 FDG study were confirmed by surgery performed 1 week later.

To our best knowledge, this is the first report on a one day protocol applying two different PET tracers labeled with two different radionuclides in a neuroblastoma patient. This study confirms previous reports stating that some neuroblastoma recurrences may have undifferentiated cells that do not express somatostatin receptors, but show high glucose consumption which has also significant (adverse) impact on prognosis.

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^{18}F-FDG PET/CT in patients with neuroendocrine tumors

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Malignant neuroendocrine tumors (NETs) constitute a heterogeneous group of rare neoplasms including the neuroendocrine islets within glandular tissues (thyroid or pancreatic) and cells dispersed between exocrine cells, such as endocrine cells of digestive or respiratory tracts, known as carcinoid tumors.

The majority of NETs exhibits an indolent growth pattern (well-differentiated tumors), but a substantial number may metastasize. The minority of NETs is aggressive and can have a highly malignant course. ^{18}F-FDG reflects the increased glucose uptake in malignant tissue. Increased FDG uptake can be seen in less-differentiated NETs mainly; it was reported, that in such cases the sensitivity of ^{18}F-FDG PET could be higher than that of somatostatine receptor scintigraphy (SRS) or MIBG scintigraphy [1]. Usual recommendation is to reserve ^{18}F-FDG PET to patients with negative results on SRS or MIBG scintigraphy. But on the contrary, Le Rest et al. [2] presented that ^{18}F-FDG PET technique identified in their group of patients with malignant paragangliomas and carcinoid tumors more abnormal sites then SRS or MIBG scintigraphy.

Precise staging is mandatory for the management of NETs. Therefore, FDG PET/CT was performed in 6 patients with NETs during one year (a total of 1590 PET/CT oncologic investigations). Co-registered PET/CT whole body images were acquired 1 hour after injection of ^{18}F-FDG (400 MBq/70 kg body weight). CT-contrast agent was applied in all patients.

Three patients suffered from abdominal carcinoid and malignant tissue was successfully detected in 2 cases of them. In one patient ^{18}F-FDG PET/CT was performed to differentiate benign and malignant etiology of pulmonary lesion and histologically was confirmed that hyperaccumulation of ^{18}F-FDG was induced by lung carcinoid. In the patient with medullary thyroid carcinoma 2 lymph node metastases with ^{18}F-FDG hyperaccumulation were detected (^{123}I-MIBG negative, one of the lymph nodes was ^{99m}Tc-DMSA(V) positive). In a patient with Merkel cell carcinoma very intensive hyperaccumulation of ^{18}F-FDG was noticed. None of the patients with carcinoid or Merkel cell carcinoma exhibits signs of hormonal hyperactivity. In a patient with medullary carcinoma high level of calcitonine was measured.

Conclusion: ^{18}F-FDG PET/CT identified malignant tissue in the majority of our patients with NETs. ^{18}F-FDG PET/CT was efficient in this small group of patients with NETs. It could be hypothesized that detection rate of NETs was improved due to usage of PET/CT fusion technique, but to confirm this assumption a larger study is needed.

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Experience and role of FDG-PET lymphoma imaging in Egypt

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Background: Positron Emission Tomography (PET) imaging using (F-18) fluorodeoxy glucose (FDG), has been introduced for the first time in Egypt in October 2004, and since that time, this technique has created a new trend in the diagnosis and management of the lymphomas, providing unique metabolic information.

FDG uptake in lymphoma is a function of increased anaerobic metabolism as well as longer residence time of FDG in malignant cells relative to most normal tissues.

Over several decades computed tomography (CT) has been the principal imaging modality for the staging and restaging of Lymphoma, although it can have shortcomings originating from its sized-based criteria, particularly, in the post-therapy status.

Aim: To evaluate the impact of FDG-PET on management of patients with lymphoma and compare its findings with the conventional investigational methods, mainly the contrast enhanced CT and to evaluate causes of discrepant findings between the two modalities.

Patients and Methods: A group of 460 consecutive patients with diagnosis of lymphoma, including 118 newly diagnosed cases, 182 cases for therapy monitoring and 160 cases with suspicious relapsed disease. The study included 288 men and 172 women with a median age of 29 years (range, 6-73 years). 311 patients of them have NHL and 149 have HL.

All patients underwent FDG PET and contrast enhanced CT within a maximum of 4 weeks time window.

A final diagnosis was established at 1850 sites for comparison between PET and CT.

Concordant PET and CT findings were regarded as positive or negative for disease. Discordant findings were defined as positive for disease, if it was confirmed by the histological examination, by the clinical progressive course or by the follow up CTs.

Results: Accuracy of FDG-PET and contrast enhanced CT was 95.8% and 85% and the Positive Predictive Value was 96.4% and 85%, whereas the Negative Predictive Value was 91.1% and 55% respectively. Agreement of both methods was excellent ($k = 0.89$). A difference with $p<0.05$ was considered significant regarding the exclusion of disease with FDG PET, compared with contrast enhanced CT.

Conclusion: FDG PET is more accurate than the conventional investigational methods; including contrast enhanced CT in evaluation of Lymphoma and can yield findings that lead to change in treatment strategy.

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Does FDG PET help in preoperative management of a thyroid nodule?

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Aim: This study was undertaken to see whether FDG –PET is useful in discriminating benign and malignant solitary thyroid nodule (STN) and aid in preoperative evaluation, noninvasively.

Materials and Methods: 89 patients with STN that were nonfunctioning or 'cold' on Pertechnetate/131-I scan were studied with 18F Fluorodeoxyglucose (FDG) – Positron Emission Tomography (PET) scanning.

Results: They were graded as A-E for the type (depending on intensity) of uptake. Group A – Consisted of 23 patients with intense FDG uptake (grade III) in the STN. On histopathology 22 were carcinoma thyroid and 1 was Hurthle cell adenoma. Group B – consisted of 5 patients with intense uptake in the wall of the nodule. On surgery 4 were malignant and 1 was a benign thyroid cyst with granulomatous reaction and chronic inflammation rich in plasma cells. Group C – consisted of 9 patients with mild FDG uptake in the nodule. All were benign on histopathology and Fine Needle Aspiration Cytology (FNAC) correlation. Group D – 51 patients with no FDG uptake in the nodule. 50 were benign nodules and 1 was Papillary carcinoma. Group E – Had 1 patient with intense FDG uptake in both lobes with no FDG uptake in the nodule. FNAC from the nodule was benign and intense uptake in both lobes was due to thyroiditis confirmed by raised AntiMicrosomal Antibodies (AMA) titre.

Discussion: The primary aim in the work up of thyroid nodules is to determine which nodules are benign and which harbor malignancy and need to undergo surgical resection. With the advent of FNA of thyroid nodules the percentage of patients undergoing surgical resection for asymptomatic benign nodules has decreased substantially. But the main problem lies in correctly differentiating benign follicular adenomas from follicular carcinoma by FNA.

Therefore a non-invasive investigation, which could preoperatively distinguish benign and malignant lesions, would spare many patients from undergoing unnecessary surgical resection of benign lesions. It would also be helpful in patients who are at high-risk for surgical morbidity-as an unnecessary surgery can be avoided [1,2]. PET differs from conventional imaging techniques like USG, CT, MRI in that they rely on morphological alterations for tumor detection. In contrast, PET is a functional imaging technique that relies on in vivo visualization of lesional glucose metabolism. The value of FDG- PET is already established in the follow- up of those thyroid cancers with elevated TG levels and negative radioiodine scans.

This prospective study was undertaken to see the usefulness of PET in differentiation of benign and malignant thyroid nodules, preoperatively.

In our study, 23 patients showed intense focal uptake in the solitary thyroid nodule. Out of these 23 patients, 22 were primary thyroid cancer and 1 was false positive. The histology of 1 was Hurthle cell adenoma. This finding is in concurrence with recent molecular studies that have shown Hurthle cell adenomas cluster with follicular and Hurthle cell cancers, rather than with benign follicular adenomas in hierarchical cluster analysis. According to this study Hurthle cell adenomas may in fact be pre malignant lesions. Grouping of hurthle cell adenoma with hurthle cell carcinoma supports this hypothesis. Thus hurthle cell adenoma showing intense FDG uptake with high SUV may point to a different biologic behavior of these masses.

5 patients showed intense uptake in the wall, consistent with focus of cancer in the wall in 4 patients and granulomatous reaction rich in plasma cells in 1.

9 patients with mild FDG uptake were colloid goiter in 1, follicular adenoma in 1 and Hashimoto's thyroiditis in 2.

52 patients showed photopenic defects. Out of these 52, 51 were benign and only one turned out to be papillary carcinoma. This was an isthmic nodule < 1 cm in size. Its small size was attributed to its false negativity.

1 of these 52, showed diffuse uptake of FDG in both lobes of thyroid, which was consistent with thyroiditis. The nodule was 'photopenic' and FNAC of the nodule was benign.

Thus, intense focal uptake, with a SUV of >3.5 in the thyroid gland suggested malignancy and minimal or no uptake of FDG was consistent with a benign lesions.

There is a growing need for a non- invasive technique that can correctly segregate the patients into benign or malignant group in all 'cold' nodules. Clearly, a solitary nodule need undergo only a PET scan as a diagnostic modality. Only those showing either B or C type of uptake be sent for further tests like FNAC and ultrasound. Those with intense FDG uptake could be sent for surgery directly. This would narrow down the surgical referral and would be more cost effective than carrying out unnecessary surgery.

Conclusion: FDG-PET can reliably distinguish the thyroid nodule into benign and malignant, when both visual interpretation and Standardized Uptake Values (SUVs) are taken into consideration. It has an important role in those nodules where the FNAC is indeterminate. In particular, FDG –PET thyroid scan plays an important in identifying malignancy in predominantly cystic lesions, which have been labeled as benign by other conventional modalities. Based on the FDG scan, after the analysis of the SUV, a patient can be directly sent for surgery or can be observed.

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Can brown fat uptake of 18F-FDG be reduced by beta-blockers?

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With the increasing application of F-18-fluorodeoxyglucose (FDG) positron emission imaging, there has been an evolving appreciation for the range of normal variants and the realization that false-positives can lead to serious consequences. One of the most common causes of a false-positive study is the uptake of FDG in areas of brown adipose tissue. BAT is generally present in deep cervical regions, including the supraclavicular areas, the interscapular and paravertebral regions, and areas near large vessels. Areas of involvement are often spatially closely related to important lymph node groups in the neck, axilla, and upper mediastinum, making critical differentiation difficult. The uptake of 18F FDG in brown adipose tissue (BAT) limits the ability of a PET scan to detect the sites of viable disease. Many studies have been done after premedication with Diazepam (benzodiazepines) to reduce the uptake of FDG by brown fat [1,2]. But they are of limited value. Thus, it would be ideal if a drug could completely reverse the brown fat uptake and thus aid in proper management of the patient.

The aim of this study is to see if by giving a single dose of a beta-blocker such as 'Ciplar' (Propranolol) 40 mg, 30 minutes prior to the FDG injection will help in reduction of brown fat uptake of 18F-FDG or not.

Materials and Methods: Patients who were referred for a PET scan, either for a pretreatment or a post treatment evaluation and who showed FDG uptake in brown adipose tissue (BAT) were taken up for this study. The total number of patients was 14. A repeat PET scan was done after a gap of at least 48 hrs after the first study. The patients were advised to keep themselves warm with adequate warm clothing on the day of the second study. 40 mg of 'Ciplar' (propranolol) was given orally 30 minutes prior to the 18F-FDG injection. A whole body PET scan was performed on a dedicated whole body PET scanner (ADVANCE, GE Medical Systems, Milwaukee, WI.), using attenuation correction with 68-Ge external pin sources.

Results: All patients showed absence of uptake of FDG in BAT, post propranolol.

Discussion: Intense FDG uptake in BAT can lead to false positive FDG PET findings. BAT is known to exhibit increased glucose uptake when the sympathetic nervous system is activated by cold stimulation. BAT has rich adrenergic innervation. BAT acts as a thermogenic organ by producing heat to maintain body temperature especially in young individuals. BAT requires glucose as a source of adenosine triphosphate (ATP). This ATP is required for fatty acid oxidation, which is the main mechanism for heat production.

In this study, we demonstrated that the intense FDG uptake in BAT can be successfully eliminated by giving 40 mg of propranolol orally 30 minutes prior to the 18-F FDG injection. Propranolol is a non-selective beta-adrenergic receptor blocking agent. It has no other autonomic nervous system activity. It is rapidly and completely absorbed from the gastrointestinal tract and undergoes extensive first-pass elimination due to its high hepatic clearence.

Conclusion: Propranolol reduces the uptake of 18F FDG in BAT and thus improves the accuracy of PET imaging.

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Yield of PET CT in evaluating cases of medullary carcinoma thyroid with elevated calcitonin levels

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Aim: To identify the yield of PET CT versus other conventional modalities (Ultrasonography and CT) in identifying recurrent or metastatic disease in cases of Medullary thyroid carcinoma with elevated calcitonin levels or suspicious recurrence.

Introduction: The surgery for medullary thyroid carcinoma involves complete thyroidectomy with bilateral nodal dissection and central compartment clearance. This extensive surgery should completely remove all foci of disease brings the calcitonin levels to near zero or remain elevated, but less than pre-operatively. A high serum calcitonin level that had previously been low following total thyroidectomy is indicative of recurrence. These levels should still be checked every 6 months, and when they begin to rise, a more diligent examination is in order to find the source.

Conventional modalities used for these are USG, CT, MRI and other radioisotope techniques. But the identification of the sites of recurrent, residual or metastatic disease is unfruitful in a large number of patients.

Materials & Methods: A retrospective analysis of the patients of medullary carcinoma of the thyroid gland referred to our department during the period of February 2005 to December 2006 was done. All post operative cases either referred for elevated serum Calcitonin levels or abnormal DMSA V study were included in the analysis. All these patients also underwent other conventional imaging modalities for detection of metastatic foci of disease.

30 patients were included in the analysis, 2 of which were referred with an abnormal DMSA V study while the rest had elevated Calcitonin levels (ranging from 249 – 30,000).

PET CT studies were obtained on a dedicated scanner (Discovery ST, GE Ltd, Milwaukee) one hour after i.v injection of 10mCi of 18F-FDG. Oral contrast was given to the patients after the injection. Iterative reconstruction was performed and images were obtained in transaxial, sagittal and coronal sections. Hardware fusion of the PET and CT data was obtained. The images were interpreted by a nuclear medicine physician and a radiologist together.

Observation: PET CT studies did not show any abnormality in the 2 patients with abnormal DMSA V studies (which were correlated to be vascular uptake in the mediastinum on Ct images and a reactive node in the neck on histology). Of the remaining 28 patients, PET CT study was negative in 7 patients and was positive in 21 patients.

In the group of patients (n=7) with negative PET CT studies, other modalities were concurrent in 4 patients while discordance was observed in 3 patients (false positive nodes confirmed histological by doing a USG guided biopsy or FNAC).

Matched results were seen in 5 of the patients with a positive PET CT study (n= 21) but 15 of the patients failed to identify any lesions on other imaging modalities.

The areas of active disease identified on PET CT studies alone were - Local recurrence in 2 patients, Active disease in the liver also seen in 2 patients, nodal metastases – neck nodes in 6 patients and 7 patients with mediastinal nodal disease (USG guided FNAC or biopsy confirmed metastatic

involvement in 11 pateints); skeletal disease in 4 patients and in the lung parenchyma in a single patient.

In the group which had concordant findings on both PET CT and other modalities nodal disease in the neck was identified in 2 patients and 4 patients had mediastinal nodes. One patient had bone involvement and 2 had lung lesions.

Discussion: A whole body PET CT study could be a single modality which would examine the entire body at a time. As seen by this study and other literature this modality has a higher sensitivity and specificity for detection of recurrence - both locoregional and metastatic as compared to other imaging modalities.

Results: PET CT identified the site of recurrent or metastatic disease in 21/28 (75%) while the other modalities identified disease only in 5 (17.86%) patients; while false positive results were obtained in 3 patients. USG was a beneficial in locating the abnormal sites on PET CT studies & help in histological confirmation.

Conclusion: PET CT helped in identifying lesions at the primary site and in the liver which were not detected on conventional imaging modalities.

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Impact of FDG PET/CT in management of patients with recurrent breast cancer - Initial experience

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Introduction: Early diagnosis with accurate restaging of recurrent breast cancer is crucial for selection of the most appropriate therapeutic strategy. Amongst many factors which tailor the decision making process for a particular management strategy, one of the most important is determining the extent of the disease. Further, in patients within higher stage, identifying limited disease from disseminated metastasis alters management, and specifies those patients with isolated lesions who are amenable to surgery and/or radiation, from those who would benefit from chemotherapy and/or hormonal therapy.

Whole body FDG PET/CT is superior to other conventional imaging modalities for defining extent of the disease by detection of distant metastasis, and distinguishing between active disease at local sites from scarred or fibrotic masses.

Aim: The purpose of the study was to evaluate the utility of FDG PET/CT in defining the extent of disease in patients with suspected recurrent breast cancer and its impact on the management of these patients.

Materials & Methods: A total of fifty-four patients in the range of 25-79 years, within the period from January 2005 to June 2006, were included in the study. All these patients were in the post treatment follow up phase with suspected recurrence. These patients were staged before performing PET/CT study, by the clinician on the basis of history, physical examination, tumor markers and conventional imaging procedures. PET/CT study was performed 60 minutes after intravenous administration of 370Mbq of 18FDG in patients, who were fasting 6 hours prior to injection. Images were acquired on dedicated PET/CT camera – discovery ST GE system. Areas of abnormal FDG concentration with their SUV values, and morphological abnormality in their corresponding CT slice were noted. Results of PET/CT scans were confirmed by further imaging, pathology, intervention, and follow up. Patients with scans positive for disease recurrence were restaged, and patients with higher stage positive disease were categorized into localized or disseminated disease. Changes in further management based on PET/CT study were noted.

Observations: Total of fifty-four patients with suspected recurrence were staged by the clinician prior to PET/CT studies. 21 of the 54 patients were categorized into lower stage (I, II or III), while 33 patients were categorized into stage IV. Based on the results post PET/CT scan, of these 21 patients in the lower stage, 11 patients were restaged (52%), while 5 patients had normal scans, and in 5 patients there was no change in the staging. Amongst the 33 patients in stage IV, post PET/CT study, 19 of them had disseminated metastasis, while in 5 patients there were no additional sites of disease detected, and 4 of these patients had normal studies. As a result of PET/CT findings management was altered in 19 of these 33 patients through change in intermodality therapeutic options (surgical versus medical management) and intramodality therapeutic options (radiation and/or chemotherapy, or hormonal). On the whole, management was altered in 30 of the total 54 patients (55%), (11 of the restaged patients, and 19 in whom disseminated disease was identified). Of these, unplanned chemotherapy and/or radiotherapy was instituted in 16 patients, surgical approach was taken in 2 patients, and additional radiation therapy was instituted in 5 patients. Futile surgeries were averted through identification of unresectable disease.

Discussion: In women who have primarily undergone treatment for breast cancer, recurrence of disease occurs frequently both at locoregional and distant sites. The clinical course of patients with recurrent breast cancer varies and is largely dependant on the extent of disease dissemination, which needs to be accurately defined for choosing the most appropriate therapy. FDG PET/CT by virtue of its metabolic activity (functional imaging) combined with morphological details enhances discrimination of abnormal areas from scar/fibrosis or detection of disease at unsuspected sites. Hence, confirmation of disease in areas which were equivocal on conventional imaging and uncovering disease at unknown sites by PET/CT determines the extent of disease and has a strong positive impact on implementing a specific treatment plan.

Conclusion: In patients with recurrent breast cancer, FDG PET/CT is a useful imaging modality for tumor detection and defining the extent of disease, hence has a significant role in determining the subsequent clinical management. In this retrospective study, treatment plan was altered post PET/CT results through restaging and identifying disseminated disease from locoregional recurrence.

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The comparison of the CT and PET/CT FDG in the diagnostics of testicular cancer

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Metastases of testicular cancer almost always spread in insidious ways and are often diagnosed in an advanced stage. In patients with this kind of neoplasm, PET with [F-18] fluorodeoxyglucose (FDG) is more sensitive and specific than the CT for detection of metastases. This value should increase if we coregister PET and CT and then fuse these images. In literature we have found only a few studies describing the value of combined PET/CT studies made by the use of FDG in this group of patients. The aim of this study is the retrospective comparison of the CT and PET/CT in the diagnostics of testicular metastases

Material Methods: In the time between March 2003 and December 2006, 126 studies were made to diagnose testicular cancer. We selected 83 studies in which we have complete information about imagining techniques such as CT with contrast media and PET/CT. PET studies were made by using the Siemens Biograf LSO scanner according to typical PET protocol. We compared the results of the particular methods of diagnostics, performing patient to patient analysis with follow up.

Results: In 55 cases (66,26%) PET/CT and CT gave consistent results. There were 32 negative PET/CT results (38,55%) and 26 CT negative results (31,32%). There was 15 patients with negative results of PET/CT and CT. In 8 patients (9,64%) PET/CT positive results corresponded with the negative CT results. In 6 patients (75%) from this group follow up confirmed PET diagnosis. In 20 patients (24,1%) CT positive results corresponded with the negative PET/CT results. There were 5 false negative PET/CT results (25%) in this group.

Conclusion: PET/CT was found to be the most valuable tool for detection of testicular cancer metastases additionally giving exact information about its localization. There is the a need to conduct a prospective study to assess the value of the PET/CT in the diagnostics of testicular cancer in connection with histopathology.

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The comparison of the CT and PET/CT FDG in the diagnostics of colon cancer in patients with an increased level of CEA marker

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Metastases of colon cancer are often diagnosed in an advanced stage. In patients with this kind of neoplasm, PET with [F-18] fluorodeoxyglucose (FDG) is more sensitive and specific than the CT for detection of metastases. The CEA level is used for monitoring the cancer but without anatomical localization of the lesions. The aim of this study was the retrospective assessment of the value of the PET/CT and CT in the diagnostics of the group of patients with an increased CEA level.

Material Methods: In the time between March 2003 and April 2005, 326 studies were made to diagnose colon cancer. We selected 32 patients referred to the PET-CT study with an increased CEA marker level who were being diagnosed for colon cancer with complete information about CT with contrast media. PET studies were made by using the Siemens Biograf LSO scanner according to typical PET protocol. We compared the results of the particular methods of diagnostics, performing patient to patient analysis.

Results: In 4 cases (14,1%) PET/CT and CT gave consistent results. There was 3 patients (9,38%) with negative results of PET/CT and CT. There were 5 negative PET/CT results (15,63%) and 29 CT negative results (90,63%). In 26 patients PET/CT positive results (81,25%) corresponded with the negative CT results. In 2 patients (6,25%) CT positive results corresponded with the negative PET/CT results. Mean CEA level in this group of patients was 28,84 ng/ml.

Conclusion: PET/CT was found to be the more valuable than CT tool for detecting colon cancer metastases in the group of patients with increased level of CEA, additionally giving exact information about their localization. There is a need to conduct a prospective study to assess the value of the PET/CT in the diagnostics of colon cancer in connection with histopathology.

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Initial Polish experience in the diagnostic utility of 18-FDG PET in the assessment of patients with multiple myeloma

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Objective: The role of whole-body PET with 18-FDG in detection of bone marrow involvement in patients with multiple myeloma was evaluated. The presence of extramedullary plasmocytomas and distribution of diffuse or focal lesions in the bones was also detected.

Materials and methods: Between November 2006 and February 2007 the whole-body FDG PET scans (60 min after intravenous administration of 370-555 MBq FDG) were performed in 15 patients (age 51-71, median 59 years, 5 males) with multiple myeloma. Five patients were referred before therapy and ten patients were referred for evaluation of therapy response (chemotherapy, radiation therapy, bone marrow transplant). Standardized uptake values were calculated to quantify FDG uptake. Results of other imaging examinations (MRI, CT, radiography), laboratory data, bone marrow biopsies and the clinical course were used for verification of detected lesions.

Results: FDG PET was able to detect medullary involvement of multiple myeloma and was helpful in differentiating between post therapeutic changes and residual/recurrent tumor cells also in assessing response to therapy. In six patients PET demonstrated a favorable treatment response by showing a decline in lesion metabolic activity. In another patients PET showed progression of disease, by demonstrating diffuse or focal bone lesions or higher lesion glucose metabolism, concordant with the clinical evaluation.

Conclusion: FDG PET is able to detect bone marrow involvement in patients with multiple myeloma. FDG PET is useful in assessing the extent of the disease at the time of initial diagnosis, contributing to more accurate staging. FDG PET is also useful for evaluating therapy response. PET can detect the extent of marrow involvement in multiple myeloma patients and could be useful in monitoring the treatment results.

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FDG-PET for assessment of therapy in lymphoma patients

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Aim/Background: A significant fraction of malignant lymphomas, both Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL), are curable but only if appropriate treatment is given. Precise classification and accurate staging of lymphoma, the selection of treatment, timely evaluation of response to therapy, as well as early detection of recurrence play a crucial role in the outcome of disease. The aim of this study was to determine the value of positron-emission tomography with 18-F-FDG (FDG-PET) for the assessment of therapy in patients with lymphomas.

Methods and materials: 57 patients with histologically proven lymphomas at IIB-IVB stages of their disease were studied with FDG-PET. In 36 patients FDG-PET were performed during or after first-line treatment (8 patients were studied prior to therapy and then second PET scans were done after 4-6 cycles of chemotherapy or after radiotherapy), in 21 patients with recurrences FDG-PET was done after few cycles of chemotherapy. All 57 patients underwent whole body FDG-PET scan following a common standard protocol. Most of patients (35|57) were studied in the standard time points: in not less than 4 weeks after completion of chemotherapy or in 2-3 months after completion of radiotherapy (I group). In 14 patients PET were performed in 10-14 days after completion of chemotherapy and in 8 patients - during the first week after completion of radiotherapy because of clinical reasons (II group). PET results were compared with findings of the conventional diagnostic methods and clinical follow-up in all cases. The median follow- up for patients was 10 months (range 3 weeks - 17 months).

Results: PET was true positive and true negative in 51/57 patients (89%). PET results were false-negative in 3 cases (in a patient with IV HD who had multifocal small lung lesions and in 2 patients with T-cell and B-cell lymphoma who had a residual mediastinal mass). PET results were false-positive in 3 cases also (in two B-cell lymphoma patients with severe mediastinal and lung fibrosis and in a patient with abdominal Burkitt lymphoma). PET altered the treatment approach in 36/57 patients (63%). Mostly management was changed in primary treated patients (25/36). There were two main management changes: from planned radiotherapy or chemotherapy to no treatment and from biopsy to no further intervention. In all six patients with incorrect results PET was performed in the standard time points after therapy.

Discussions: It is well known that accurate staging of patients with malignant lymphomas has a great clinical impact on the prognostic-dependent choice of treatment and on survival [1,2,7]. The question about an additional value of baseline pre-therapeutic PET for the accurate assessment of treatment is still unclear [1,6]. In the present series 2 patients with low-grade NHL have been previously excluded from the study because of the false-negative baseline PET scans. We presume the pre-therapeutic baseline FDG-PET should be performed in patients with low-grade or with infrequent histological types of NHL when FDG-avidity is less predictable. The baseline PET not only improves patients staging, but also may provide the important information for future accurate assessment of treatment.

A key factor for successful evaluation of treatment is an appropriate time point for PET. It is generally accepted today that PET may be performed in 4 weeks after completion of chemotherapy and in not less than 3 months after radiotherapy [3,5]. Quite often such regime of scanning is not available in lymphoma patients because of some important clinical reasons.

According to our findings we suggest if the baseline PET was done the accuracy of post-treatment PET doesn't decrease despite of the shorter interval between the completion of chemotherapy and the second scanning.

Radiation-induced inflammatory reaction is the most frequent reason of false-positive PET especially in patients with mediastinal and pulmonal lesions [4]. We suggest that post-radiotherapeutic PET in lymphoma patients should be performed in the shortest time after completion of radiotherapy before the non-specific treatment effects appear. In this study levels of FDG accumulation in the area of radiation were higher (SUVmax up to 2,7) in patients who were examined in standard time after radiotherapy.

Conclusions:

1) Whole body 18F-FDG PET is an efficient method for assessment of therapy in lymphoma patients (accuracy was 89%). PET results have altered management in 36/57 (63%) patients.

2) Baseline pre-therapeutic PET scan has a significant value for the accurate assessment of treatment: the comparison of baseline and following PET findings may decrease the level of false-positive results, false-negative results associated with different histological types of lymphomas can be excluded at the pre-therapeutic stage. The performance of PET at short interval after chemotherapy (in 10 days) is possible if baseline PET was done.

3) The intensive FDG uptake in the area of fibrosis is a most frequent reason of false-positive results in lymphoma patients after radiotherapy. The careful comparison of PET and CT results and knowledge of radiotherapy ports helps to exclude incorrect PET conclusions.

4) PET scan obtained in the shortest time after completion of radiotherapy allows correct assessment of treatment and may play an important role for future therapeutic decisions.

However, larger studies are needed to appreciate these results.

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Role of FDG-18 PET/CT in the diagnosis of unknown primary cancer

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Background/Aim: Carcinoma of unknown primary (CUP) syndrome is defined as the presence of histologically proven metastatic disease without evidence of a primary tumor. It is heterogenous group of tumor with myriad clinical presentations. Conventional cancer therapeutic strategies based on tumor location, tumor grade and tumor stage is often not easily applicable to CUP. This results in a clinical dilemma with negative prognostic impact. The aim of this retrospective study was to evaluate the benefits of dual modality positron emission tomography-computed tomography (PET-CT) in patients with CUP.

Materials and Methods: From July 2003 to August 2006, a total of 24 consecutives patients with CUP were investigated with PET/CT. There were 13 men (age range 36-84 years, mean age of 57 years) and 11 women (age range 39-75 years, mean age of 58 years). All the patients had histologically proven metastatic disease with negative or inconclusive findings from conventional diagnostic procedures, including clinical examination, laboratory tests, projectional and cross-sectional imaging and endoscopy where indicated. Further investigations were performed based on PET/CT findings to arrive at the final diagnosis and the patients were followed-up for a minimum of 8 months. PET/CT was performed as a single examination using Siemens Biograph scanner. The PET images were evaluated by one of six nuclear medicine consultants (experience ranging from 4 to 15 years) and the CT images were interpreted by one of four consultant radiologists. These sites of abnormal FDG uptake were then further investigated, usually endoscopically or with percutaneous biopsies to reach a final histological diagnosis.

Results: In the group of patients who presented with metastatic cervical lymphadenopathy (n=14), PET-CT identified suspicious areas of abnormal FDG accumulation in 10 patients, for which 9 received histological confirmation of a primary tumor, giving a primary tumor localization rate of 64% within the group. PET-CT further revealed additional sites of metastases in one of these 9 patients. PET-CT did not identify any potential primary tumor site in 4 patients and 1 of these patients died during the study period and was shown to have primary lung tumor on autopsy.

In patients who presented with extra-cervical metastases (n=10), PET-CT identified suspicious areas of abnormal FDG accumulation in 7 patients. In 5 of these patients, the sites of abnormal FDG uptake were confirmed to harbour the primary tumor on histology, giving a primary tumor localization rate of 50% within the group. Furthermore, PET-CT further revealed additional sites of metastases among 4 of these 5 patients which resulted in increase tumor stage. In the rest of the 2 cases, PET-CT depicted FDG avid colonic tumors that were proved to be adenomas on biopsy. PET-CT did not identify any potential primary tumor site in 3 patients and 1 of these patients died during the study period with no primary tumor found on autopsy. The SUVmax of the confirmed primary tumor sites in both group (both cervical and extra-cervical metastases) ranges from 2.4 to 30.8 with a median of 9.9. The overall primary tumor localization rate in both groups is 58%.

Discussion: CUP accounts for up to 5 to 10% of all cancer patients and generally have poor survival rate. By definition, patients present with metastatic disease with the primary site remaining elusive using conventional diagnostic strategies. Several postulations had been raised and they include: small subradiologic primary tumor, primary tumor hidden within metastases and primary tumor involution after metastatic seeding, to list a few. Furthermore, it has been shown that knowledge of the primary tumor and tumor dissemination has direct impact on patient care and survival rates. FDG-PET has been proven to be highly effective in localising primary tumors with detection rate between 24 to 53%

with grade Ia level of evidence. However, the lack of accurate anatomical correlation remained a challenge to conventional FDG-PET, until the arrival of PET-CT co-registration systems.

The cervical region is the commonest presenting site for CUP. In our study, high primary tumor localization rate was noted in patients with cervical metastases. Furthermore, PET-CT also contributed by providing functional nodal staging for these head and neck tumors with important treatment planning implications. Within the group with extracervical metastases, the primary tumor localization rate was lower. However, the usefulness of PET-CT appeared to lie in the detection of additional metastatic sites, especially when patients presented with extra-cervical lymphadenopathies (4 patients). Revelation of these additional metastases resulted in increase tumor stage in all 4 patients. The overall primary tumor localization rate in our entire study cohort of 58% compares favourably to the reported range of 43-67%. PET-CT failed to identify any potential primary tumor sites in 7 of our patients. Of note is that the primary tumor site remained undetectable in all these 7 patients during the follow-up period except during autopsy in 1 patient. This is in-keeping with the high sensitivity of PET-CT in tumor detection and also suggests that a negative PET-CT potentially has a negative predictive value on subsequent primary detection.

Conclusion: Our retrospective study shows that PET-CT can play an integral role in CUP with both diagnostic and therapeutic impact.

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Unexplained rising Carcinoembryonic antigen (CEA) and the utility of F18-FDG PET-CT in recurrent colorectal cancer: Preliminary experiences in Thailand

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Background: Colorectal cancer is one of the fifth leading sites of cancer in Thailand. After surgery was performed, serial determinations of the plasma carcinoembryonic antigen (CEA) concentration are the most frequently used method for the detection of recurrent disease.

Although carcinoembryonic antigen (CEA) is the most cost-effective tumor markers for monitoring recurrent colorectal cancer after initial surgery and chemotherapy, it lack specificity with a false positive rate of approximately 10-30% and rising of CEA level does not always prove the presence of recurrent disease. Therefore, an invasive technique is needed to confirm the disease and select the patients eligible for a potentially curative resection of the lesion.

18F Fluorodeoxyglucose positron emission tomography has been introduced as a novel technique highly sensitive for the detection of recurrent disease. This is no doubt that early detection has an influence on therapy, especially resection of a solitary liver or lung metastasis. This led to the reimbursement of the use of PET-CT for this indication in Thailand. However, there is limited data on the utility of F18-FDG PET-CT for detection of recurrent colorectal cancer in patients with increasing CEA level. To better define the possible benefits of FDG PET-CT in this issue, the authors retrospectively reviewed 32 cases of patients with suspected colorectal cancer.

Material and Methods:
Patient population: A retrospectively study of suspected recurrent colorectal cancer patients who underwent 18F FDG PET-CT at National Cyclotron and PET Centre, Chulabhorn Cancer Centre, Research Institute from September 2006 to February 2007 was analyzed. Thirty two patients (20 males, 12 females) of aged 19 to 90 years (mean age 60.65 years) were studied after having received informed consent. These patients had conventional diagnostic work-up with normal or equivocal results. The mean CEA level at the date of PET-CT was 45.42 ng/ml.

Imaging procedures and data analysis: All the patients fasted for more than 4 hours before the whole body PET-CT scan. The PET-CT imaging (Biography 16, Siemens) was performed approximately 50 minutes following intravenous injection of an average dose of 12 mCi 18F-FDG.

Data analysis: All PET-CT images were evaluated by visual interpretation of the nuclear medicine physicians and diagnostic radiologists who were not blinded to available data. Lesions that were seen by PET-CT with disease became obvious, were considered to be true –positive findings. When no abnormality was seen on PET, this was considered to be true-negative results.

Statistic analysis: From this data base, data was analyzed using StataCorp. 2003 (Stata Statistical Software: Release 8.0. College Station, TX: Stata Corporation). Exact test was used for comparison of data. A p-value of less than 0.05 was considered to indicate a statistically significance.

Results: Thirty –two patients, 25 patients had rising CEA level, whereas 7 had normal CEA level. FDG PET-CT was abnormal in 16 of 32 patients (15 had abnormal CEA level, 1 remained normal CEA level), 15 of 16 (93.75%) patients with rising CEA level have the positive PET-CT findings. The median CEA level is 11.86 ng/ml. The results are summarized in Table 1.

TABLE 1. CEA LEVEL AND PET-CT FINDINGS

	PET-CT findings		
CEA level	Positive	Negative	P. Value
CEA group; N (%)			0.0831
increase	15 (93.75%)	10 (62.50%)	
normal	1 (6.25%)	6 (37.50%)	
CEA level (ng/ml); median (range)	11.86 (28-613)	17.4 (6.9-94.47)	0.3827

Discussion: Although our preliminary results show no statistically significant correlation between the CEA level and PET-CT findings, in the group of patients with increasing CEA level demonstrates positive PET-CT findings 93.75% whereas 62.50% shows negative findings. The results of this study shows that in the majority of patients with rising CEA level and normal or equivocal conventional imaging, whole body 18F FDG PET-CT is useful for diagnosis.

Study limitation: The current study was also limited by histopathology results and the small number of patients included. Therefore, it might have decreased the authors' powers to detect the true different significance. Further large sample size studies for the utility of 18F FDG PET-CT in suspected recurrent colorectal cancer with increasing CEA level and normal or equivocal anatomical imaging results in Thailand are needed.

Conclusion: These preliminary results suggest that 18 FDG PET-CT is useful technique for detecting suspected recurrence colorectal cancer with increasing CEA level and normal or equivocal anatomical imaging results.

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^{18}F-FDG scan in well-differentiated thyroid cancer patients with increased thyroglobulin antibody but negative I-131 total body scan

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Background/Aim: It is generally accepted that ^{18}F-FDG PET scan is a valuable tool for evaluation of well-differentiated thyroid cancer patient who has increased level of serum thyroglobulin (Tg) but negative I-131 total body scan [1,2]. However, there are a group of patient who present with normal thyroglobulin level but increased thyroglobulin antibody (anti Tg) level and negative I-131 body scan. The persistence of thyroglobulin antibodies after thyroidectomy and radioiodine ablation probably indicates the presence of recurrent disease in these patients [3]. Presently, ^{18}F-FDG PET has been suggested for patients with negative I-131 total body scan and elevated Tg level for the detection of both local recurrences and metastases of differentiated thyroid cancer. However, the value of ^{18}F-FDG PET for patient management is still unclear for patients with negative I-131 total body scan but increased thyroglobulin antibody levels. Therefore, the aim of this prospective study was to evaluate the usefulness of ^{18}F-FDG PET in these patients.

Methods and materials: We intend to evaluate the usefulness of ^{18}F-FDG in well-differentiated thyroid cancer patients whose blood samples show increased anti Tg level but negative I-131 total body scan and normal serum Tg level. We plan to investigate at least 15 patients. All patients with differentiated thyroid cancer were treated by total or near total thyroidectomy. One month after total/near total thyroidectomy, we performed I-131 total body scan. Baseline serum Tg and antiTg are also evaluated. If there is any visible remnant of thyroid tissue or evidence of metastases, thyroid remnant ablation or metastatic treatment with I-131 is performed. Then 6 months later I-131 total body scan, serum Tg and antiTg will be re-evaluated to search for any evidence of residual thyroid tissue of metastasis. If all 3 investigation results are concordant, patient will then be re-evaluated every 6 month period with only serum Tg and antiTg. If there is an increasing of blood level of anti Tg above 200 U/ml, I-131 total body scan will then be performed. If I-131 total body scan shows no evidence of tracer uptake and serum Tg shows normal value (Tg≤10 ng/ml during serum TSH > 30 mIU/ml) ^{18}F-FDG PET/CT scans were performed. All of these patients underwent ^{18}F-FDG PET/CT examination,60 min. after application of 0.12 mCi/kg of ^{18}F-FDG, whole- body images were acquired on an using an Biograph 16 (Siemens) and images were visually interpreter by two nuclear medicine physicians. Suspicious lesions were evaluated with regard to pathology, CT, MRT or clinical follow-up.

Results: Because PET/CT scan machine has only just been installed in our department, until now we have performed 6 of these patients. Four of six patients (4/6) have positive PET/CT finding. The finding in these 4 patients were proven to be true positive: by pathology (n=2) and CT (n=2). In contrast, 2 out of 6 (2/6) patients, showed no pathologic FDG uptake. The finding in these 2 patients were proven to be true negative by CT. We plan to investigate at least 15 patients and the rest of results will be show in the International conference on Clinical PET and Molecular Nuclear Medicine (IPET-2007).

Discussion: The prevalence of circulating thyroglobulin antibodies (anti Tg or antithyroid peroxidase) was increased nearly 3-fold in patients with differentiated thyroid cancer (DTC) compared with the general population (40% vs. 14%) [4,5]. Serum anti Tg (with or without antithyroid peroxidase) was present in 25% of DTC patients and 10% in the general population. It has been recently observed that the present of circulating antithyroid antibodies in previously treated for DTC may be associated with a persistent or relapse of disease, implying that anti Tg themselves could play some clinical role in DTC patients. In one study, 49% of patients with undetectable serum Tg concentrations and serum anti

Tg concentrations of 100 U/ml or more had a recurrence when compared with only 3% of patients with undetectable serum Tg concentrations and serum anti-Tg antibody concentrations of less than 100 U/ml [6]. Our data show that the persistence of detectable circulating anti Tg suggested the presence of recurrent or metastatic tissue in some patients and ^{18}F-FDG PET/CT is useful imaging modality to detect the lesions.

Conclusion: This preliminary results of our study shows that ^{18}F-FDG PET/CT is useful for localizing recurrent or metastatic lesions in well-differentiated thyroid cancer patient who present with normal thyroglobulin level but increased thyroglobulin antibody level and negative I-131 body scan. Thus, ^{18}F-FDG PET/CT might be a valuable diagnostic tool in these patients.

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Bilateral pheochromocytomas and neuroendocrine tumor of pancreas demonstrated with FDG-PET/CT in a patient with von Hippel-Lindau syndrome: A case report

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Aım/Background: Von Hippel Lindau disease (VHL) is a hereditary cancer syndrome in which affected individuals are at risk for developing tumors in a number of organs, including the kidneys, brain, spine, adrenal glands, eyes and pancreas. Here we reported a case of a VHL syndrome with CNS hemangioblastoma, bilateral pheochromocytomas and pancreatic tumors and F-18 FDG PET/CT scan findings

Methods and Materıals: A 21 year old female with no significant past medical or family history except iodine hypersensitivity (not suitable for CT contrast agents), presented initially with a CNS hemangioblastoma, which was completely resected. Her laboratory analysis showed increased 24-hour urine vanillylmandelic acid (VMA) and plasma metanephrine, and Ca19.9 levels. Other laboratory parameters were normal. She subsequently underwent a staging FDG PET/CT to exclude the possibility of other cancers of VHL syndrome. Whole-body image was obtained 60 minutes after the intravenous administration of 15 mCi of F-18 FDG on a Siemens Biograph 16 PET/CT scanner.

Results: Whole body F-18 FDG PET/CT scan revealed an nonmetabolic area in the right cerebellar hemisphere secondary to tumor resection. Additionally, PET/CT study also showed abnormally increased FDG metabolism in the adrenal glands bilaterally (Figure 1) and pancreas (Figure 2) consistent with bilateral pheochromocytomas and pancreatic tumor. Bilateral pheochromocytomas and neuroendocrine tumor of pancreas were verified after surgical exploration.

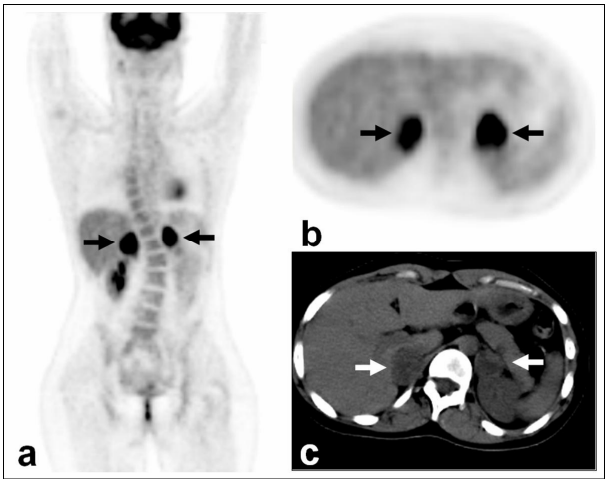

FIG. 1. Coronal and axial F-18 FDG PET (a, b) and axial unenhanced CT (c) images revealed marked degree of abnormal FDG uptake in the adrenal pheochromocytomas bilaterally.

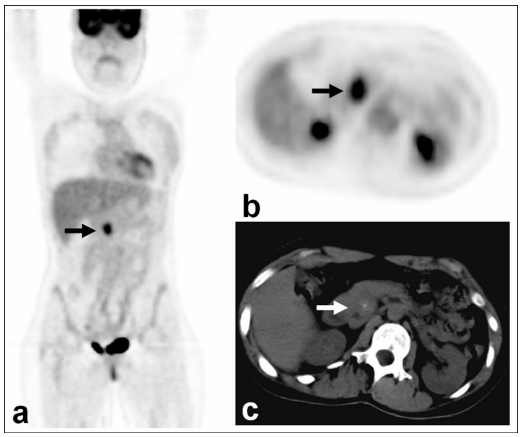

FIG. 2. Coronal and axial F-18 FDG PET (a, b) and axial unenhanced CT (c) images showed marked degree of focal abnormal FDG uptake in the pancreatic tumor.

Dıscussıons: VHL is a rare autosomal dominant familial cancer syndrome caused by germline deletions or mutations in the VHL tumor suppressor gene located on chromosome 3p25. Symptoms often begin in the second to third decades of life. Symptoms caused by VHL depend on the organ involved [1].

Criteria for the diagnosis of VHL include: more than one hemangioblastoma in the CNS, one CNS hemangioblastoma and visceral manifestations of VHL, or one manifestation and a known family history of VHL. Important manifestations of VHL are: hemangioblastoma [of retina, CNS (especially cerebellum), kidney, bladder and pancreas], angioma (of retina, liver and spleen), hemangioma (of kidney and bone), lymphatic sac neoplasm of labyrinth, cyst (of lung, kidney, epididymis, pancreas, liver, spleen and bone), hypernephroid tumor of epididymis, renal cell adenoma and carcinoma, testicular germ cell tumor, papillary cystadenoma of broad ligament, pheochromocytoma (adrenal and extra-adrenal), paraganglioma, rhabdomyoma of heart, syringomyelia, meningioma, neuroendocrine tumor of pancreas, nevus and café au lait spot of skin, carcinoid of the common bile duct. Although half of VHL pheochromocytomas present bilaterally, these patients requires lifelong biochemical and radiological screening for pheochromocytoma., and there is a high incidence of recurrence after surgery [2].

Tumors at various sites are demonstrable by using different imaging modalities, including US, CT, MRI, and angiography. The preferred examination depends on the site or organ involved. CT and MRI best depict intracranial lesions, and MRI is more appropriate for examining spinal lesions. Retinal tumors are visualized best on US, the kidneys and pancreas can be imaged by using US and/or CT scans. The limitation of various techniques depends on the size of the tumor and on problems with atypia. CT and US findings are not reliable in differentiating cystic renal cell carcinomas.

Nuclear Medicine studies, such as; bone scan, renal scan (to assess renal function prior to resection of renal tumors), I-131 MIBG (for diagnostic and therapeutic approach), F-18 DOPA PET, F-18 FDG are increasingly valuable in VHL. PET with F-18 FDG provides an indication of metabolic activity of tumors.

Conclusıons: In VHL, tumors can be found at various sites. Numerous imaging modalities, including US, CT, MRI, bone and I-131 MIBG scintigraphy and angiography should be used together to demonstrate all foci. However, FDG PET/CT as a whole body imaging modality might be used alone instead of multiple other conventional imaging modalities in diagnosing most of the neoplasms associated with VHL.

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The role of FDG - PET imaging in lymphoma (Egyptian experience in 460 cases)

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Introduction: The evolution of combined chemotherapy regimen and radiation therapy strategies has resulted in high overall survival rates in patients with Hodgkin's Lymphoma (HL) and certain subtypes of Non-Hodgkin's Lymphoma (NHL) particularly diffuse large cell lymphoma. Staging has an important role in the management of most malignancies and can serve to assess prognosis and to define therapy for patients with lymphoma. In particular, accurate staging and determination of response (re-staging) can determine whether radiation therapy may be indicated for an individual lymphoma patient**.**

Position Emission Tomography (PET) imaging using (F18) fluorodeoxy glucose (FDG) has the potential to provide physiological information that can be useful in staging as well as monitoring response to therapy. FDG uptake in tumors is proportional to the glycolytic metabolic rate of viable tumor cells related to increased metabolic demand for glucose. Alteration in FDG uptake as measured by various methods including visual and quantitative analyses, provides useful information on response to anti-tumor therapy, especially using the standardized uptake value (SUV), which is a semi-quantitative method that measures FDG uptake in the tumor per volume, normalized to the injected activity per body mass. Quantitative PET imaging may have its greatest impact in fact in the evaluation of therapy response.

Patients and Methods: A group of 460 consecutive patients with a confirmed diagnosis of lymphoma were referred to us for imaging between 01/2005 and 06/2006. All PET studies were performed at the International Medical Center (IMC). The study subjects included 288 men and 172 women with a median age of 29 years (range, 6-73 years).

Three hundred eleven patients (311 pt.) were proven histo-pathologically to be (NHL) and one hundred forty nine patients (149 pt.) to have (HL).

A total of one hundred eighteen (118) studies were performed for initial staging in patients who had been subjected to histopathology evaluation, one hundred eighty two (182) studies were performed for therapy monitoring and one hundred sixty (160) studies were performed for re-staging and follow up after disease remission or suspicious relapse.

Of the 182 studies performed of therapy monitoring, seventy four (74/182) were performed for therapy response prediction after the first cycle of chemotherapy, thirty six (36/182) were performed for mid-course response assessment after 3 cycles and seventy two (72/182) were performed after therapy completion and disease remission confirmation. FDG-PET was performed at least three – four weeks after the last cycle of chemotherapy and at least 3 months after the completion of radiation therapy to minimize false-positive results.

Imaging: Patients fasted at least 4 hours prior to intravenous injection of FDG, 2 MBq /Kg, for an average dose of 150 MBq (4 mCi). Imaging was performed with a C-PET plus system (Philips). This system has an axial field of view of 24 cm. with transverse resolution of 8 mm and axial resolution of 6 mm full width at half maximum. Data obtained from the six crystals were used to reconstruct the image on flight via RAMLA software.

Emission and transmission acquisitions were commenced simultaneously, one hour after injection. Six to seven bed positions were usually done, each bed position lasted about 8-9 minutes.

All PET images were interpreted at the time of the study by two nuclear medicine doctors who had access to the clinical data. Standardized uptake value (SUV) and target-to-background ratio (T/B ratio) were determined. In order to be able to compare the PET images of different patients, the PET data calibrated to activity concentration are normalized for image analysis with respect to injected activity and patient weight. The resulting transverse parametric slices represent a standardized measure of the regional tracer concentration at the point of uptake. This is referred to the "standardized uptake value" (SUV). Based on review of literature, we considered a value of SUV > 2.5 and (T/B) ratio > 1.5 to be abnormal**.**

Results & Discussion: Initial staging: 12 out if 118 patients (10.2%) have been upstaged. Assessment of therapy after the first cycle revealed that 54 out of 72 patinets (75%) had CR and only 4 developed relapse later. Whereas 18 out of 72 patients (25%) had residual disease, 16 of them (90%) had never achieved CR within the first year. After the third cycle; 29 out of 36 patients (80%) had CR, 7 of them (20%) had residual disease, and 6 of these 7 patients(85%) never achieved CR within the first year. After the sixth cycle 40 out of 74 patients (54%) had complete remission, the remaining 34 (46%) had residual disease, 30 patients of them (90%) never achieved CR within the first year. For re-staging 103 out of 160 (64%) PET and CT were matched (63 negative and 40 positive); 32 of the remaining patients PET detected additional nodal involvement than does CT with upstaging in (20%) while 25 patients CT detected lesions that missed on PET, but only 5 of them proved by biopsy. Hence, PET correctly down-staged 20 patients (12.5%).

Accuracy, Positive Predictive Value and Negative Predictive Values of FDG-PET were (95.8%, 96.4% and 91.1%) vs (85%, 85% and 55%) for CT.

Our findings regarding the accuracy of PET are similar to those obtained by other investigators.
PET is significantly more accurate than CT for lymphoma staging, restaging and therapy monitoring. Similarly, when the PET and CT results were combined, it was found that out of the 5 patients with positive PET findings and negative CT findings after therapy, 4 experienced local relapse or progression of disease 3-12 months after re-staging; while none of the 30 patients with negative FDG-PET findings and positive CT findings had experienced disease relapse 6-15 months later.

Conclusion: FDG-PET has a potential role in accurately staging disease, in predicting response to therapy, re-staging and follow up of malignant lymphoma.

This role has the potential to affect both the initial choice of chemotherapy and the decision to alter management based on the initial response to therapy. PET performed early in a chemotherapeutic regimen has demonstrated a role in identifying patients who will experience relapse and may require change of treatment strategy, but attention to the timing of the scan in relation to chemotherapy and radiotherapy is crucial.

Is screening ^{18}F FDG PET/CT scan appropriate in unknown primary with rising tumour marker and normal conventional imaging?

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Introduction: Present-day medical practice generally assumes that early detection of cancer offers the best chance of a good outcome. Tumor markers are used in oncology to help determine the presence of cancer. An elevated level of a tumor marker can indicate cancer, however there can often also be other causes of the elevation. Generally serum tumor markers are not recommended as a screening tool for the presence of malignancy, especially in an asymptomatic population. This is related to the lack of desired specificity of tumor markers in general as well as the low prevalence of cancer in the general population. With few exceptions, the measurement of serum tumor marker in condition of high incidence of cancer in population or with clinical and physical examination are of benefit. A lot of patients who have a high level of a screening tumor marker become anxious about beign affected by cancer. The aim of this study was to evaluate whether PET/ CT scan is of advantage to detect a primary cancer in this condition.

Methods: We retrospective reviewe a database of 257 patients who underwent PET/CT between July 2006 and February 2007 at the National cyclotron and PET center at Chulabhorn Cancer Centre. Patients referred for rising tumor marker levels and unknown primary cancer are included in this study. Seven patients matched the inclusion criteria and were reviewed for age, gender, tumor marker levels, anatomical imaging finding (CT and MRI) and PET finding.

Result:

TABLE 1. PATIENTS DATA AND CLINICAL RESULTS

Patient	Clinical	Tumor Marker	Anatomical imaging	PET finding
1. Male 70 y-o	FUO 2 months	CEA 12.1 CA 19.9 215.7	CT whole body normal	PET/CT normal
2. Male 71 y-o	No	CEA 12.1 CA 19.9 215.7	CT whole body normal	PET/CT normal
3. Female 56 y-o	No	CEA 12.8 CA 125 42.6	CT chest and whole abdomen normal	PET/CT normal
4. Male 82 y-o	No	CEA 25	CT chest and whole abdomen normal	PET/CT normal
5. Female 45 y-o	No	AFP 10 CA 19.9 80	MRI upper abdomen normal	PET/CT normal
6. Male 45 y-o	No	AFP 8.6	MRI abdomen normal	Mildly increased uptake at left iliac bone(CT lytic and sclerotic) (Figure1)
7. Female 52 y-o	Pulmonary embolism rt. lung	CEA CA 125 56.73		Increased activity at right pulmonary thombus
				Mild increased uptake at right upper lung with thick wall cavity (Figure2)

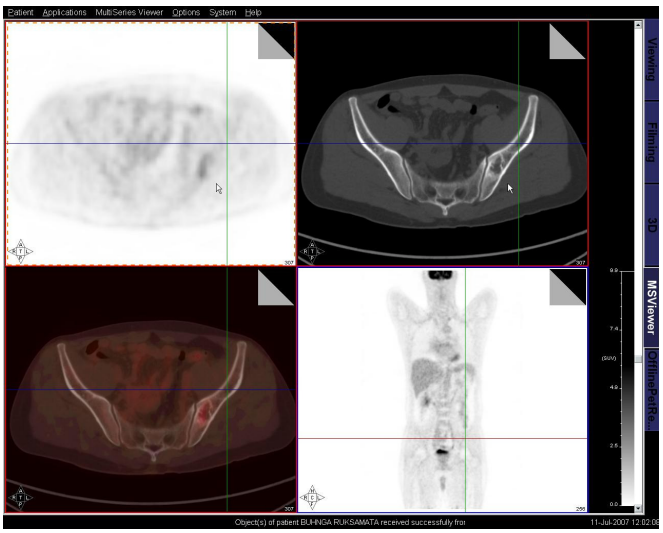

FIG. 1. Case number 6.

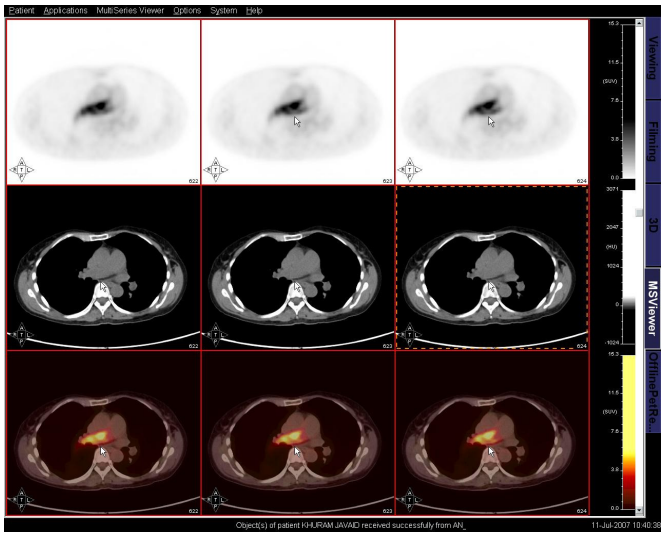

FIG. 2. Case number 7.

The result showed that PET/CT was normal in 5 cases and show that PET/CT did not provide additional information over CT. In two cases PET was positive: case # 6 and Case # 7. Case #6 was still normal after a clinical follow up of 6 months. In case #7, PET showed the presence of a glucose avid lesion in the right lung. Contrast CT confirmed the presence of a blood clot and the patient was treated with wafarin and claxane. The clinical follow up showed improvement. The high levels of serum Ca-125 could well be explained by lung infarction.

Conclusion: Although our data are small, PET/CT scan prove not to provide more information for detecting unknown primary camcers in patients with rising tumor marker and normal conventional imaging. Despite the excellent sensitivity of PET-CT in tumor detection interpretative pitfalls must be taken into account.

POSTER SESSION II

CLINICAL SPECT

SPECT in PET era: Do gamma cameras still have a role in the oncological diagnosis and management?

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In a Nuclear Medicine Department, usually 50-60% of the gamma camera studies are performed to stratify oncological patients or their follow-up. Planar & SPECT studies are more affordable for the social security budget in Latin America than those from PET. Cost of nuclear medicine non-PET studies are in the range of 150-200 $USD, while a PET is nearly 1500-1800 $USD.

Moreover, the large armamentarium of radiopharmaceutical compounds available for the gamma cameras, with specific labelled antibodies turn the mentioned instrument in a more versatile tool than PET. QC of the radiopharmaceutical, the gamma camera (planar & Spect) performance and protocol of the study should be strictly kept to obtain a reliable set of images. If the former are followed the study will be still incorporated in the diagnostic algorithm of the oncological patient. Consideration must also be taken in account that although more PET centers are being built, few have the baby cyclotron capacity that will allow the use of other compounds than FDG-F18. Expertise training is not fully achieved.

Aim: To show the important role that the gamma camera studies still have in the diagnostic algorithm of the oncological patient.

Materials & Methods: We led a retrospectively analysis of the last five years of patients consulting in our general Nuclear Medicine Department (with planar & Spect facility). Our Nuclear Medicine Center is a representative General Clinical University Center, in a 500 bed Hospital situated in the Capital City of Argentina (with a population of 11.000.000 inhabitants).

Fifteen-thousand (15.000) patients were evaluated in these five years. The study demand was in decreasing order as follows: bone scintigraphy, diagnostic & therapeutic thyroid studies, cardiological pathologies, pulmonary studies, renal investigation, infectious diseases, oncological gallium, mamoscintigraphy, gastroenterological scans, sentinel node, radiosinovectomies, octeotride-In-111, MIBG-I-131, bone pain palliation & others.

Results: The outcomes of bone scans classified the studies as belonging to primary oncological or metastasic disease with which diagnosis a therapeutic decision was installed.[1] Scintimamography with Sestamibi or Tl-201are in increasing demand.[2] Thyroid pathology was resolved in 98% of the cases with the mentioned instrumental survey. Indirect or direct pulmonary results either allowed oncological lung intervention (semiquantitative method) or diagnosed possible clinical complications that threatened patient's survival such as thromboembolic (TEP). Cardiac perfusion studies Rest, stress or gated as well as ventricular ejection fractions were systematically required for the follow up of oncological therapies. Dynamic and static renal studies are requested for primary pathology or as a consequence of immunosuppressive drugs. Lymphomas patients are still surveyed with Gallium scans as the first step in the diagnostic algorithm & for the follow up.[3] Immunosuppresed patient's quiz is to differentiate oncological pathology from over-infection. Therapeutic Beta radiopharmaceuticals for lymphoma require a whole body scan with gamma emitters previous to attempt treatment. Diagnostic & follow-up of patients under bone-pain palliation treatment require whole body gamma camera scans

Sentinel node detection & gamma probe instruments with the appropriate molecule use the gamma camera in aid of the adequate surgical approach (breast cancer, head & neck surgery, melanoma & vulvar carcinoma)

Radiolabelled monoclonal studies appeared to reflect oncological activity & predict therapeutic response such the case of Octeotride-In111/ Tc99m [4] as well as MIBG-I131 performed as planar & Spect imagings which still produce reliable diagnostic images for identifying neuroendocrinological & paraganglioma tumors.Anatomical identification will now be also available through the SPECT/CT capability of this new challenging instrument.

Conclusions: The evaluated patients satisfactorily had a diagnosis or follow up survey with planar or SPECT examinations. Less than 1% were also PET users in which not more than a 50% had a different result or a therapeutical criteria variation. Thus Health cost did not suffer an increasing burden through Nuclear Medicine practices. Cost & availability of the FDG-F18 in the few PET Centers installed in our country are the major drawbacks to choose PET as the eligible diagnostic oncological image.

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Role of planar and SPECT ^{99m}Tc -MIBI scintigraphy in breast cancer patients before and after neoadjuvant chemotherapy

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Aim: The purpose of this study was to evaluate clinical application of planar and SPECT ^{99m}Tc-methoxyisobutylisonitrile (MIBI) scintigraphy as a method for assessment of MDR in breast cancer patients, correlation of these results with P-gp overexpression and objective treatment response.

Methods and materials: In a study 22 women, 35-68 year-old with positive for breast cancer mammography and cytological tests, suitable for neoadjuvant chemotherapy were included. Two or three cycles of neoadjuvant chemotherapy were administered (FEC in 15 and CMF in 7 patients). Planar and SPECT ^{99m}Tc-MIBI scintigraphy was performed before and after chemotherapy (740-925 MBq, dose, applied i.v.). Focal ^{99m}Tc-MIBI uptake in breast cancer lesions was used as a scintigraphic criterion of abnormality. Tumor/Background uptake (T/B Index) was calculated. Immunohistochemistry was carried out after surgery for P-gp detection in all cases. The degree of expression was evaluated according to the semi quantitative score analysis from 0 to 4.

Results: Pretreatment planar imaging was true positive in 21 patients, false positive – in 1 case (with breast cancer and mastopathy), false negative – in 1 patient (with wide tumour necrosis and deep location in the breast). SPECT imaging was true positive in 22 patients, false positive in 1 case, no false and true positive results. Additional tumour lesions were visualised in 3 patients with multifocal BC on the tomographic slides. Sensitivity was 95% (21/22) and 100% (22/22) respectively for baseline planar and SPECT primary cancer detection. Axillary lymph node metastases were visualised together with the primary tumour in 9 patients out of 19 with nodal involvement. Pretherapeutic ^{99m}Tc-MIBI uptake in the tumour was intensive in the early planar images and showed marked retention on the tomographic slides in 21 cases independently of the P-gp expression. In 16 cases T/B Index was>/=1.50. P-gp overexpression was positive in 40.8% and negative – in 59.2% of patients. There was no correlation of P-gp expression rate and type of histology and/or hormonal receptors. Neither P-gp overexpression nor histological type of receptor status of tumours showed a significant relationship with T/B Index on the baseline investigations. Our results are similar to the data, published recently [1,2]. Objective clinical response included 2 complete remissions, 1 patient with 50% tumour reduction and 12 patients – with minimal response (20-35% reduction). No clinical response was obtained in 7 cases.

Discussions: Some clinical results corresponded with posttherapeutic ^{99m}Tc-MIBI uptake. Decreased ^{99m}Tc-MIBI uptake was associated with response to therapy while progressive disease was correlated with stable or increasing tracer uptake. In 2 patients with complete response T/B Index corresponds to a tumour activity uptake equal to the normal tissue uptake; P-gp expression was negative; 3 cycles of FEC were applied. In 7 patients with no change of the disease and 3 patients with minimal response, T/B Index rate was the same or with minimal reduction: =/<0.15. It is more difficult to interpret the results of the rest 10 patients with partial and minimal response after neoadjuvant chemotherapy – in 7 cases P-gp expression was negative, in 3 cases – P-gp was positive, T/B Index was reduced >/=0.20.

Conclusions: In conclusion the data of the present study confirm that SPECT acquisition improves sensitivity of planar ^{99m}Tc-MIBI scintigraphy. SPECT imaging correctly assessed multi focal disease in 3 patients diagnosed additional tumour lesions. In one patient planar imaging missed a primary breast cancer with deep location near the chest wall and poor vascularisation. Significant correlation between P-gp overexpression and T/B Index rate obtained before and after neoadjuvant chemotherapy

was not found in our patients. These results are similar to the data, obtained in other studies [3,4]. Nevertheless it was seen that tracer uptake was reduced >/=0.20 in 54.5% (12/22) patients: in 2 cases with complete response, in 1 case with 50% tumour reduction and in 9 cases with minimal response. It suggests that ^{99m}Tc-MIBI scintigraphy may be used for response monitoring purpose.

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The primary clinical application study of technetium-99m labeled ethylenedicysteine-deoxyglucose in tumor glucose metabolic imaging

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Aim: to evaluate the primary clinical application value of ^{99m}Tc labeled ethylenedicysteine-deoxyglucose (^{99m}Tc-EC-DG) in tumor imaging.

Methods and materials: ^{99m}Tc-ECDG was achieved by means of adding the required amount of ECDG and tin (II) chloride to the pertechnetate. Radiochemical purity was assessed at radio-thin-layer chromatography. 60 patients underwent ^{99m}Tc-EC-DG imaging, 51 patients with malignant tumor and 9 patients with benign lesion. 7 cases of 51 patients with malignant tumor underwent ^{18}F-FDG imaging contrastively. The patients fasted 6 hours and then underwent the ^{99m}Tc-EC-DG imaging after the injection of 25mCi ^{99m}Tc-EC-DG intravenously, the planar and tomographic imaging was acquired 2 hours and 4 hours after the injection, and the ratio of tumor to normal tissue was calculated. In ^{18}F-FDG imaging, the dose of ^{18}F-FDG injected was 5mCi, T/N ratio was calculated as well as ^{99m}Tc-ECDG imaging. The machine used in this study is Axis dual-headed coincidence SPECT of PICKER company of USA. The imaging interpretive criterion is that if the radioactivity in the lesion is higher than that in the normal tissue visually, the imaging is determined to be positive. Otherwise, it's negative.

Results: in ^{99m}Tc-EC-DG imaging, 1 case of lymphoma and 1 case of hepatic cell cancer have false negative result. 6 cases have false positive result among 9 cases of benign lesion. The sensitive of ^{99m}Tc-EC-DG imaging is 96.1%, the specificity is 33.3%, the accuracy is 86.7%. Among 11 malignant cases with lymph nodes metastasis, only 1 case's metastatic lymph node was visualized. In ^{18}F-FDG imaging, all 7 cases with malignant tumor have positive result. The average T/N ratio of ^{99m}Tc-EC-DG imaging and ^{18}F-FDG imaging are listed in table:

The average T/N ratio of ^{99m}Tc-EC-DG and ^{18}F-FDG imaging

	Malignant tumor	Benign lesion
T/N ratio of ^{99m}Tc-EC-DG at 2h	1.92±0.73	1.56±0.48
T/N ratio of ^{99m}Tc-EC-DG at 4h	2.22±0.91	1.64±0.60
T/N ratio of ^{18}F-FDG	7.38±2.60	

Discussions: In our primary clinical application study, ^{99m}Tc-EC-DG imaging has high sensitivity in diagnosing of malignant tumor, but its specificity is low. For specificity, ^{99m}Tc-EC-DG imaging has no advantage compared with ^{18}F-FDG imaging. The imaging of 4 hours after injection is better than that of 2 hours of ^{99m}Tc-EC-DG imaging. 7 cases with malignant tumor underwent ^{18}F-FDG imaging and all had true positive result. The images of ^{18}F-FDG is better than that of ^{99m}Tc-EC-DG, and its T/N ratio is higher than that of ^{99m}Tc-EC-DG imaging of the same patient. The difference between ^{99m}Tc-EC-DG imaging and ^{18}F-FDG imaging is caused by the resolution of collimator of ^{99m}Tc-EC-DG imaging and the resolution of electronic coincidence detection, and also caused by the slower blood clearance of ^{99m}Tc-EC-DG compared with ^{18}F-FDG.

^{18}F-FDG imaging has high accuracy in seeking lymph node metastasis. In our study, among 11 malignant cases with lymph node metastasis, mediastinal lymph node was visualized in only 1 case, the main reason was the slower blood clearance of ^{99m}Tc-EC-DG, thus the cardiac blood pool, mediastinal vessel and other big vessels interfered the visualization of lymph node metastasis. Other reasons maybe that the metastatic lymph node is too small to be imaged, and the degree of tumor aggression in lymph node is low. These reasons may limit the clinical application of ^{99m}Tc-EC-DG imaging in some aspect.

EC-DG can not go through the blood brain barrier and can not accumulate in brain. The low radioactivity in brain is profit to image the head and neck tumor. In our study, the high radioactivity in kidney was found, and this may interfere the visualization of the lesions around kidney.

Conclusions: From our study we agree that ^{99m}Tc-EC-DG glucose metabolic imaging for malignant tumor is feasible, compared with ^{18}F-FDG imaging, both the image quality and diagnostic ability of ^{99m}Tc-EC-DG is not so good as ^{18}F-FDG. But, ^{99m}Tc-EC-DG imaging is easy and cheap to perform on the conventional nuclear medicine machine instead of PET. Our study is a very primary application study of ^{99m}Tc-EC-DG imaging, it's necessary to perform more cases of different kind of cancers to deeply explore its value in clinical application.

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Preliminary results of the evaluation of 99mTc-EDDA/HYNIC-Tyr^3-octeotride prepared from lyophilized kits vs 111 In-DTPA-octeotride with SPECT images in patients with metastatic neuroendocrine tumors in the National Cancer Institute of Bogota-Colombia

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Many tumors express somatostatin receptors, which allow their detection with radiolabeled somatostatin analogs. The 111In DTPA-Octreotide, (Octreoscan ^{R}), is considered one of the standard procedures given its high affinity for somatostatin receptors and its good performance for the pretreatment assessment and staging of neuroendocrine tumors.

The metodology described by Dr. Decristoforo for development and labeling of other somatostatin analogs based on Tyr^3-Octreotide (TOC), using hidrazinonicotinic acid (HYNIC) as ligand for ^{99m}Tc and EDDA as coligand yielded good results in preclinical studies. This later allowed its development as a freeze – dried kit formulation. We will conduct a prospective, cross-over study to evaluate the quality of image obtained with both ^{111}In DTPA-Octreotide and ^{99m}Tc-HYNIC-TOC and the cost per study in patients with metastatic neuroendorine tumors.

Methods: The HYNIC-D-Phe^3-Tyr^3-Octeotride peptide with a chemical purity > 98% was synthesized by piChem (Graz, Austria). ^{99m}Tc-pertechnectate has been obtained from the CIS BIO ELumatic 99Mo/99mTc generator, the other reagents were provided by Aldrich-Sigma.

Liophylized formulation and labeling: EDDA solution 20 mg/mL was dissolved in sterile water and mixed using a 0.22 um filter with disolved Tricina + Manitol (40 mg/mL and 100 mg/mL in water, respectively) and then purged for 15 min with N_2. HYNIC-TOC was disolved in 10% ethanol to a concentration of 0.5 ug/uL. $SnCl_2$ was dissolved in HCl 0.1N (previously purged with N_2) to a concentration of 1 mg/mL. Both solutions were then added together with Manitol +Tricina + EDDA. 1.0 mL of the mixture was then dispensed in sterilized vials to obtain a final concentration of 20ug of HYNIC-TOC, 10 mg of EDDA, 20 mg of Tricina and 50 mg of Manitol which was then frozen at -50 ^{o}C and lyophilized during 24 h. 1.5 mL of Na_2HPO_4 0.2M and 0.8-1GBq /2mL of ^{99m}Tc-petechnectate were sequencially added to the freeze-dried kit of EDDA/HYNIC-TOC followed by incubation in a boiling water bath for 20 min at 92 ^{o}C.

Radiochemical purity was determined by thin-layer cromatograpy using ITLC-SG and three solvents: metil-etil-ketone, PBS and acetonitrile-water (1:1).

Plasma protein binding was determined by incubating 50 uL of labeled peptide (500 uCi and 1 ug of peptide) with 450 uL of human plasma at 37^{o}C during 15, 30 min, 1, 2 and 4 h. For the negative control, 50uL of peptide were mixed with 450 uL of SSN 0.9% and incubated under the same conditions. After incubation, 25 uL of peptide were added in a column of Microspin^R G50 and centrifuged at 3000 rpm for 2 min. The collected eluate was counted in a NaI counter. Protein-bound peptide was calculated as a porcentage of eluate obtained from the column.

After a 4-hour incubation, plasma stability was determined by adding of 25 uL of peptide to 25 uL of acetonitrile and then centrifuging at 2000 g for 2 min. The eluate was analized using ITLC at the same conditions described for radiochemical purity. The kits were tested for sterility and pyrogenicity by conventional pharmaceutical procedures

^{111}In-DTPA-octreotide it will be prepared from kits commercial available (Octreoscan^{R}) according to the parameters of the manufacturer

Imaging for ^{99m}Tc-HYNIC-TOC was performed 2 h after injection of 500-600MBq using a dual head gamma-camera (E.cam. SIEMENS), low energy high-resolution collimators and a 15% energy window set at 140 Kev. SPECT adquisition parameters were: 128 projections (64 per detector, 20 seconds each) in a 128x128 matrix. ^{111}In images were obtained 4 and 24 hours post injection of 150MBq using a medium energy parallel-hole collimator, 20% energy window set on both 172 and 246 keV peaks. The same SPECT adquisition parameters were used but with 30-sec projections. Interpretation of whole body and SPECT images was performed by two independent nuclear medicine physicians. The evaluation of the image would be based on a) the appearance of each observed lesion derived from neuroendocrine tumors, b) Number of lesion observed in each study c) The ROI technique for semi-cuantitative analysis of main organ and tumor uptake. ROIs were draw over observed dominant lesion and tumor-to-normal tissue ratios for this lesion were calculated.

Will be included patients with diagnosis previously established by histophatology and inmunohistochemical analyses with metastatic neuroendocrine tumors, between 18 and 70 years of age. We calculated a size of sample of 46 dominant lesion using the program STATA 8,2.

Results and Discussions: The dissolution of ^{99m}Tc-HYNIC-TOC kit was fast and complete. Showed >90% radiochemical purity; 3%-10% plasma protein binding and plasma stability was > 4h. Kits were tested for pyrogenicity obtaining values < 1 UE/dosis

Up to date, already have been recruited twelve patients, six women, age range 41-57 and six men age range 22-70, three (n=3) patients did not complete the studies. The number of lesion dominant observed for both studies was nine.

For 99mTc-HYNIC-TOC the number of lesion was: one in 4 patients, two in 1 patients, more of three in 4 patients, and for ^{111}In-DTPA-octreótide was: one in 5 patients, more of three in 3 patients and in 1 case we are not observed any lesion. In all the cases these difference were statistically significant ($p<0.05$). The semi-quantitative analysis showed small difference tumor-to-normal tissue ratios between 99mTc-HYNIC- TOC and both 111In-DTPA-octreotide (25.94 vs. 22.10) ($p>0.76$) by no statistically significant.

Conclusion: So far the results revealed a higher number of lesion observed for 99mTc-HYNIC-TOC than those obtained with ^{111}In-DTPA-octreótide but in tumor-to-normal tissue ratios were no statistically significant. Is necessary to complete the study to obtain a definitive result, so that to the date the size of sample is very small

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Carcinoid tumours, diagnosis and staging using 111-In DTPA octreotide - Preliminary experience

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Carcinoid tumors constitute a group of neuroendocrine neoplasms that develop mostly in the gastrointestinal tract. Their potential malignancy depends on their site of origin.[1] Imaging plays a very important role in the localization and staging of the tumors and also in monitoring the response to treatment.[2] Their diagnosis is based on a combination of anatomic and functional techniques, depending on the tumor type and localization.[3] These techniques include mainly especial laboratory tests, endoscopy, ultrasonography, CT, MRI and somastatin receptor scintigraphy.

The incidence and frequency of this type of tumors in Colombia are not completely known, but it seems that they occupy about 2% of the gastrointestinal malignant tumors. There are more than 80 centers of nuclear medicine in this country, but due to the high cost of the procedure it is not done as regularly as needed. In our institution this diagnostic procedure is practiced since 1998, and our experience is comparable to that of other local centers.

This study evaluates the role of 111-In Octreoscan in the detection and following of 12 patients (aged 27-76 years) with suspected or confirmed Carcinoid tumors between 2004 and 2007. The scintigraphic findings were correlated with laboratory results, MRI, CT, clinical and surgical outcomes.

The administered average dose of In-111 OctreoScan (Mallinckrodt Medical, Inc., St. Louis, MO) was 5.0 mCi (185 MBq). The patients were well hydrated with ample fluid intake prior to, and for 1 day after, radiopharmaceutical injection to increase the renal excretion, and to reduce radiation dose. An ADAC gamacamera was used and whole-body anterior and posterior images were acquired at 4 hours and 24 hours with SPECT scan at 24 hours. A matrix of 64 x 64 and 64 projections were used, together with a medium-energy, high-resolution collimator. Images were analized by at least two nuclear medicine specialists.

The diagnostic of carcinoid tumours, most of them midgut carcinoids, was confirmed in seven patients after surgery treatment and Octreoscans were negative in the following period, although in one of them the laboratory findings remained abnormal. Two patients had increased uptake of octreotide in the suspected preoperative focus and correlated well with the surgery findings and laboratory results. Of the last three patients suspected to have a carcinoid tumor, one presented with focal lesions in liver and resulted in a metastasis of medullary carcinoma of thyroid gland, (Fig. 1). In one patients with negative scans the presence of pancreatic tumour (pancreatic pseudocyst) was confirmed, and the last patient, with positive scan, had a neuroendocrine well diferenciated tumor.

We concluded that although our preliminary study included a very small number of patients, Octreotide scintigraphy played an important role in the detection of primary or metastatic carcinoid tumours and that during the follow up period most of them remained disease free as shown by imaginological and biochemical studies. We believe that by including this type of useful studies in the context of our national health system, the presently high cost of the procedures will be lowered thus permitting us to offer to these oncological patients a better diagnostic and follow up methodology and allowing a more complete evaluation of their response to treatments and to discover in them new sites and/or other types of endocrine tumors.

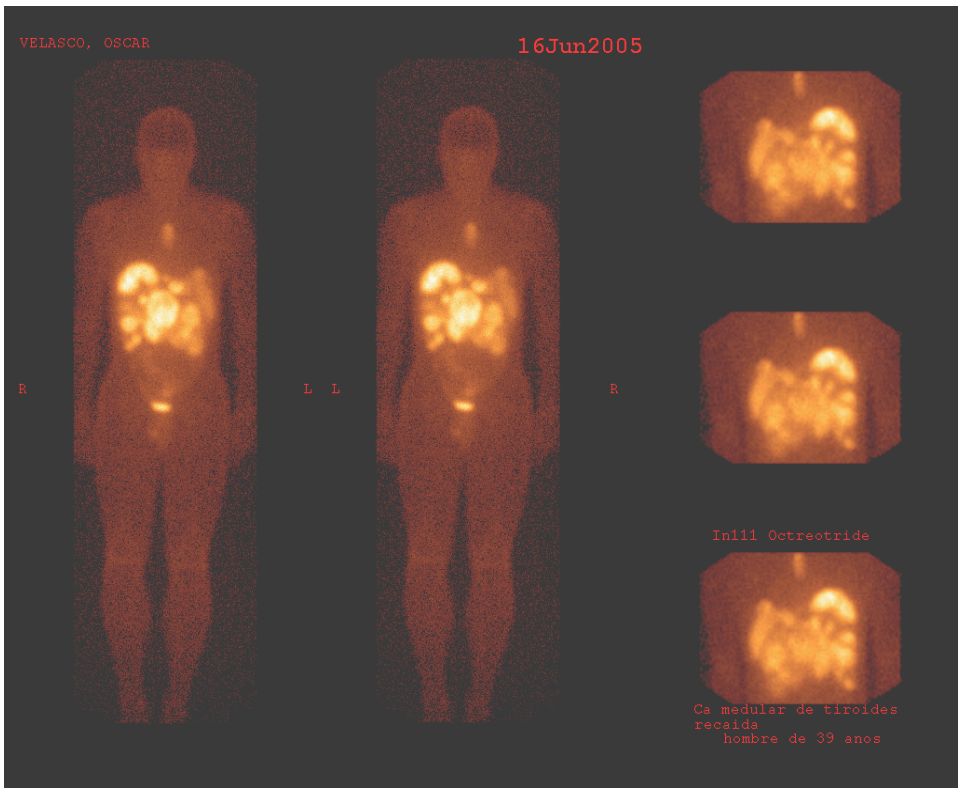

FIG. 1. Metastatic involvement of liver.

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Internal dosimetry of iodine 131 using SPECT images in patients with thyroid carcinoma in the Instituto Nacional de Cancerologia, Bogota, Colombia

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Background: with the purpose of determining the iodine 131 biodistribution in patients with thyroid cancer, a patient-specific dosimetry protocol was developed and applied, using the administration of a tracer (diagnostic) amount of this radionuclide and the methodology of the Medical Internal Radiation Dose (MIRD). The dosimetry method consists in a determination of the maximum tolerated activity that will deliver 2 Gy to the blood (A_{max}), and the corresponding ablative lesion dose (D_{lesion}).

Methods and Materials: fifteen patients with thyroid-stimulating hormone (TSH) level of 30 mU/L and a suppressed iodine diet were orally administered with a tracer activity (111-148 MBq). Then, the radioiodine kinetics in blood and whole body were determined collected one milliliter of heparinized blood samples at 2, 4, 24, 48 and 72 hours and using an uncollimated NaI detector with anterior and posterior counts at 5 minutes, 2, 4, 24, 48 and 72 hours. The activity determination in lungs, stomach, thyroid and metastatic targets were done using a region-of-interest (ROI) technique. Individual ROIs were drawn on both anterior and posterior projections at 2, 4, 24, 48 and 72 hours. Calculations were based on the geometric mean of anterior and posterior counts, including corrections for photon scatter, attenuation, septal penetration, and other effects in the gamma camera.

Results: the data were fitted to multicomponent exponential retention functions or in closed compartment models (Figure 1) using the Organ Level Internal Dose Assessment (a software program OLINDA, Vanderbilt University). OLINDA is U.S. Food and Drug Administration (FDA) approved as a device and includes S values specific to 10 phantoms and 5 organ models for more than 800 radionuclides, and, subsequently, the calculation of radiation absorbed doses to the different organs and tissues.

Discussions: The internal dosimetry method implemented has the advantage of being ambulatory and the tumor doses was prescribed for those cases in which tumor uptake give ablative lesion dose D_{lesion} of 300 Gy.

Conclusions: The internal dosimetry is useful in determine the optimal amount of administered activity in radioiodine therapy, so that the absorbed doses to the organs of interest turn out to be the optimal, without overcoming the maximum tolerated dose in red marrow and the maximum tolerated dose (MTD) to the lungs.

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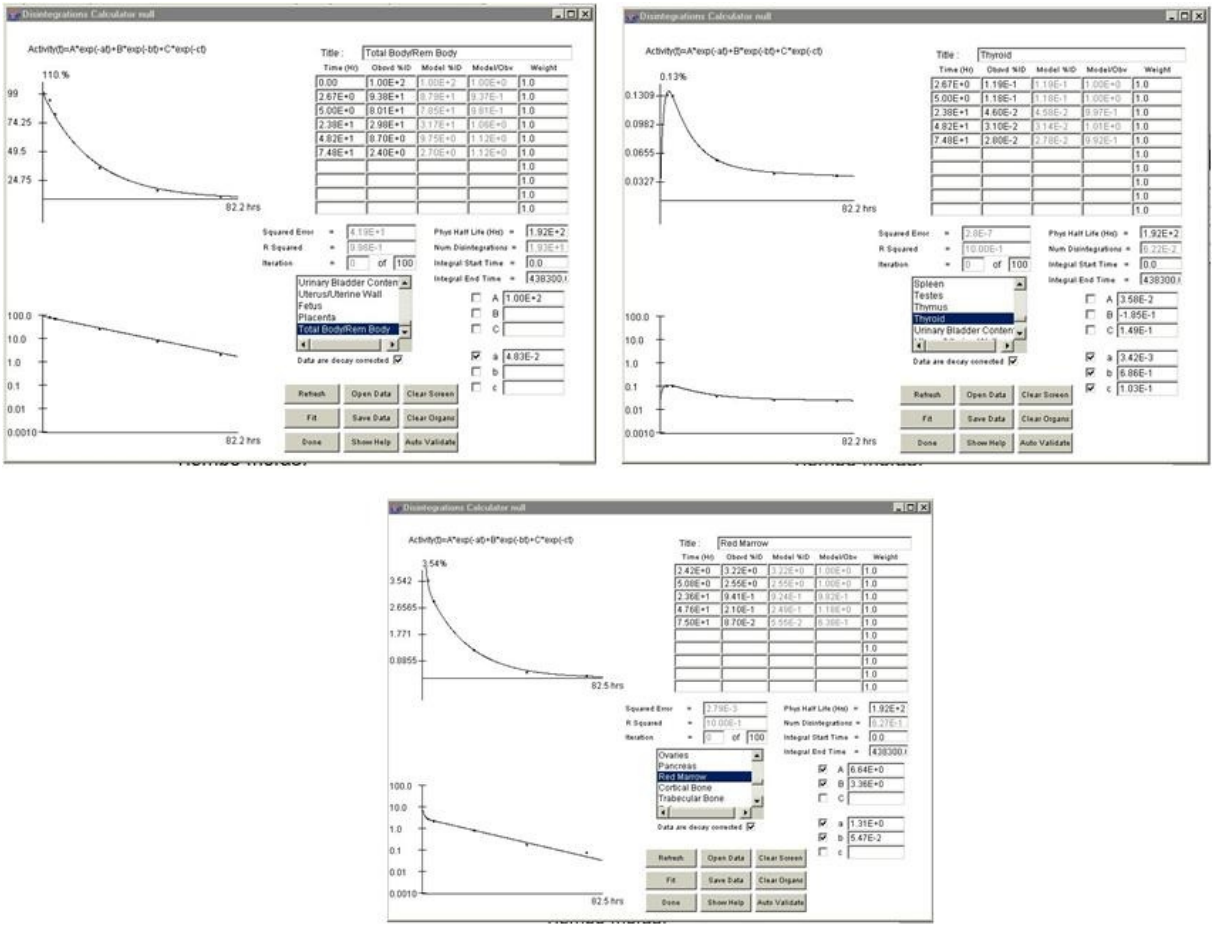

FIG. 1. Time-fraction of injected activity data. Whole body, tyroid and blood were fitting using OLINDA software.

Use of Ga-68-labeled peptides and PET for diagnosis and therapy monitoring in oncological patients

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Abstract: The purpose of these studies was to evaluate and compare the pharmacokinetics of [^{68}Ga]-labeled peptides in oncological patients. First, [^{68}Ga]-DOTATOC was used in patients with metastatic neuroendocrine tumours (NET) planned for [^{90}Y]-DOTATOC using dynamic PET. Second**,** dynamic PET studies with a ^{68}Ga-Bombesin analog, the ^{68}Ga-BZH$_3$, were performed in patients with gastrointestinal stromal tumors (GIST) to investigate the impact of the complementary receptor scintigraphy on diagnosis and the potential of a radionuclide treatment. Furthermore, dynamic ^{18}F-Fluorodeoxyglucose (FDG) studies were performed in the same patients.

Materials and Methods: 23 patients (90 lesions) with confirmed metastatic NET were enrolled in this study. Dynamic [^{18}F]-FDG and [^{68}Ga]-DOTATOC PET scans were performed on two different days in the same week. 9 patients were examined with [^{68}Ga]-DOTATOC PET only. Furthermore, 17 patients with GIST were studied with ^{68}Ga-BZH$_3$ and FDG on two different days within one week. All GIST patients were scheduled for adjuvant therapy with Glivec due an unresectable primary or recurrent GIST or due to metastatic disease. Dynamic PET scans using ^{68}Ga-BZH$_3$ and FDG were obtained on two different days within one week. Multivariate analysis was used for the evaluation of all kinetic data. SUV´s were calculated and a compartment model (two-tissue) with a blood component as well as a non-compartment model based on the fractal dimension (FD) was used for data evaluation of both tracers.

Results: SUV was defined as the SUV measured in the last frame (55-60 min p.i.) of the dynamic series, for each tracer.

NET-results: The median SUV uptake was 7.9 for [^{68}Ga]-DOTATOC and 5.7 for [^{18}F]-FDG. The selection of patients for the [^{90}Y]-DOTATOC therapy was based on the uptake of [^{68}Ga]-DOTATOC. Multiple linear regression analysis was applied to determine the effect of each kinetic parameter (k1-k4, VB) on the global SUV of both radiotracers.

The analysis of the DOTATOC data demonstrated the highest F-ratio for k1 (F-value: 18.34, p.<0.0001) (receptor binding), followed by k3 (F-value: 3.96, p= 0.0506) (cellular internalization) and followed by VB (F-value: 1.49, p= 0.2267) (fractional blood volume) when using the global [^{68}Ga]-DOTATOC uptake (SUV) as a target variable.

The analysis of the [^{18}F]-FDG data revealed the highest F-ratio for k3 (F-value: 9.72, p=0.0109) (phosphorylation), followed by VB (F-value: 2.39, p=0.1532) and k1 (F-value: 1.38, p=0.266) (influx).

The comparison of the global SUV, the k1-k4 and the FD (fractal dimension) for [^{18}F]-FDG and for [^{68}Ga]-DOTATOC did not show any statistically significant correlation. The only parameter that demonstrated a significant linear correlation between the two radiotracers was the VB.

GIST-results: Fourteen of 17 pts (25/30 lesions) were positive in FDG imaging, whereas ^{68}Ga-BZH$_3$ demonstrated an enhanced accumulation in 7 of 17 patients (8/30 lesions) with GIST. Thirteen lesions were confirmed by histology and the remaining 17 by follow-up. One recurrent tumor in the stomach could not be delineated in FDG but showed an enhanced ^{68}Ga-BZH$_3$ uptake. The median SUV for ^{68}Ga-BZH$_3$ was 3.3 in comparison to 7.9 SUV for FDG. Best subset analysis demonstrated that the global SUV (55-60 min p.i.) for FDG was primarily dependent on k3, followed by k1. Multivariate analysis did not show a significant correlation between the kinetic parameters (k1-k4, V_B, SUV) for FDG and Bombesin.

Conclusions: [^{68}Ga]-DOTATOC is a promising tool for the evaluation of the expression of SSTR$_2$ in NETs. The combination of [^{18}F]-FDG and [^{68}Ga]-DOTATOC dynamic-PET studies provides different information regarding the biological properties of lesions in patients with metastatic NETs planned for [^{90}Y]-DOTATOC therapy. While the global [^{68}Ga]-DOTATOC uptake is influenced mostly by k1 (receptor binding), the global [^{18}F]-FDG uptake is mostly influenced by k3 (phosphorylation). Only patients with enhanced [^{68}Ga]-DOTATOC-uptake (>5.0 SUV) were referred to [^{90}Y]-DOTATOC therapy.

^{68}Ga-BZH$_3$ may be helpful in a subgroup of patients with GIST for diagnostic reasons, e.g. in case of a negative FDG scan and suspicion of viable tumor tisse. However, radionuclide therapy does not seem to be indicated according to these preliminary results because in general the peptide uptake was not high enough for that purpose. Furthermore, the physiologically enhanced Bombesin-uptake in the pancreas may cause additional problems in case of radionuclide therapy.

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Tc99m-sestamibi scintimammography: Usefulness of semi-quantitative evaluation

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Aim: Tc99m-sestamibi scintimammography (SMG) is a well-established technique in the detection of metabolically active breast tumors. However, only a few studies have attempted an objective differentiation of breast masses based on quantification of radiotracer uptake. This study was done with the aim of establishing a semi-quantitative parameter using Tc99m-sestamibi to differentiate malignant from non-malignant breast masses.

Methods and Materials: One hundred and three female patients, aged 16 to 71 years (40.4 ± 12.5) with palpable breast masses were investigated using Tc99m-sestamibi scintimammography. Scinti-imaging was performed under a dual head gamma camera in the anterior supine and prone lateral projections. Imaging was started 10 min after intravenous injection of 20 mCi (740 MBq) of the radiotracer into a foot vein and each image was of 10 minutes duration. During processing, an irregular region of interest (ROI) was first positioned over the area of abnormal tracer uptake (if any) in the lateral view of the breast. An identical ROI was positioned over an uninvolved area over the same breast. Counts over these two ROIs were compared and the tumor to background (T:B) ratio was determined (Fig. 1). In the absence of any focal tracer concentration in the breast, T:B ratio was considered as 1.0. The final diagnosis of each patient was established either by FNAC or histopathology following surgery.

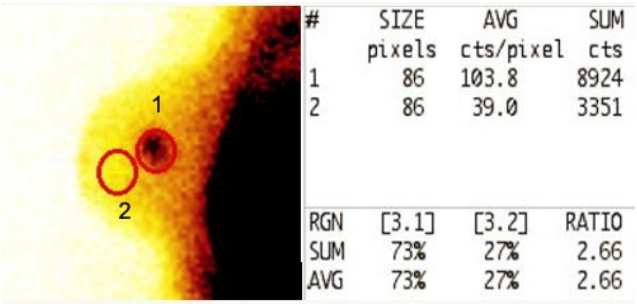

FIG 1. Regions of interest marked over breast mass (1) and normal background (2), with respective counts and T:B ratio displayed in the right panel

Results: Of the 103 patients investigated, 60 had breast masses with a T:B ratio less than 1.8 (0.58 – 1.76; 1.23 ± 0.25). Fifty-seven of these had benign breast conditions, while three were diagnosed to be malignant on histopathology. In the remaining 43 patients, T:B ratio was 1.80 or above (1.80 – 6.0; 2.56 ± 0.72). Thirty-four of these patients had carcinoma of the breast confirmed on FNAC, while the remaining 9 showed benign conditions (1 fibroadenoma, 1 tubular adenoma, 2 fibrocystic disease and 5 inflammation). Using a T:B ratio of 1.80 as the minimum cutoff value for identifying malignancy, Tc99m sestamibi SMG was found to have a sensitivity, specificity, accuracy, PPV and NPV of 91.9%, 86.4%, 88.3%, 79% and 95% respectively in differentiating cancer from benign conditions of the breast.

Discussions: Previous studies have suggested that a higher grade of malignancy is associated with increased in-vivo tumoral uptake of Tc99m Sestamibi [1]. Subjective assessment of "abnormal" sestamibi uptake in breast masses may be erroneous, with false positive concentration of the tracer reported in fibroadenomas, acute/ granulomatous inflammation, trauma and nonmalignant proliferative ductal disease [2]. Delayed imaging alone may not distinguish these conditions from carcinoma, and also prolongs study time, presenting logistic problems in a busy nuclear medicine department with limited resources. Several semi-quantitative techniques have been reported to improve the accuracy of SMG, with T:B ratios of 1.13 to 3.48 at 10 min post-injection indicative of carcinoma [3,4]. In this study, a T:B ratio of 1.8 used as an arbitrary cutoff value to differentiate malignant from benign breast masses showed a high degree of sensitivity and specificity, consistent with the published literature. However, fibroadenomas and inflammatory lesions may still show increased sestamibi concentration, resulting in a false positive diagnosis of carcinoma. Of the five inflammatory masses with T:B ratio > 1.8, four had undergone needle aspiration within 3 days prior to the study. The fifth showed irregularly increased, non-focal uptake of sestamibi. Only 3/60 patients (5%) with T:B ratio <1.8 in the breast mass were diagnosed to have breast cancer. Two of these masses were < 15 mm in size, and only one was more than 20 mm. False negative sestamibi uptake in this solitary case could be due to p-glycoprotein expression or poorly differentiated tumor type [5].

Conclusions: Semi-quantitative measurement of the tumor to background (T:B) ratio of radioactive counts significantly improves the sensitivity, specificity and accuracy of Tc99m sestamibi scintimammography in differentiating malignant from non-malignant breast masses in a single phase study.

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Differential radiotracer uptake patterns on dual phase scintimammography

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Aim: Scintimammography (SMG) is a well-established technique in the detection of metabolically active breast tumors. However, most studies use single phase SMG, which has a lower specificity for malignant breast conditions. This study was done with the aim of identifying the pattern of uptake and retention over time of Tc99m-sestamibi in various malignant and non-malignant breast masses on dual-phase SMG.

Methods and Materials: Fifty-four female patients, aged 20 to 80 years (41.2 ± 13.9) with palpable breast masses were investigated using Tc99m-sestamibi scintimammography. Static images (10 min each) were acquired 10 min after intravenous injection of 20 mCi (740 MBq) of the radiotracer into a foot vein, under a dual head gamma camera, in the anterior supine and prone lateral projections. In patients where tracer concentration was identified in the breast/ axillary region, a second set of images was acquired 2 hours later. A final diagnosis was established either by FNAC or histopathology following surgery.

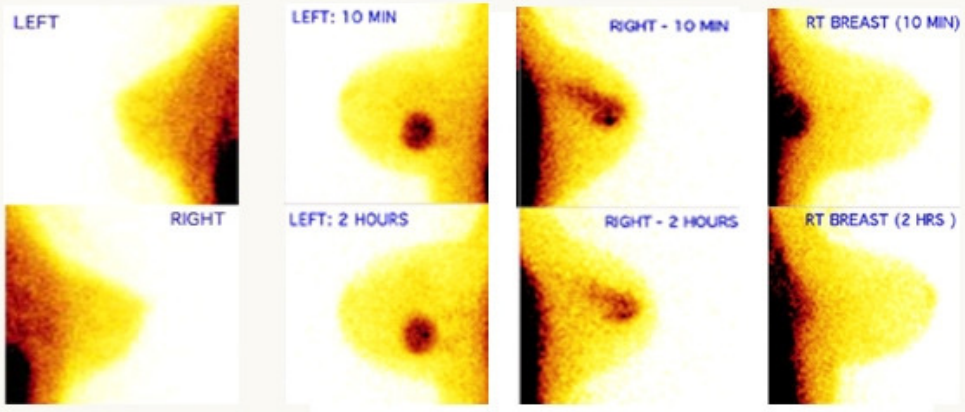
Results: Of the 54 patients investigated, 30 were diagnosed to be benign (18 fibroadenoma/ fibrocystic disease, 8 inflammatory, 2 galactocoele and two with benign aspirate), while 24 were malignant. Ten out of 30 benign breast masses showed no tracer uptake, while 13 showed mild/ irregular tracer uptake at 10 minutes. In the latter group, 9 showed washout at 2 hours while 4 showed retention (2 fibroadenoma, 1 granulomatous inflammation, 1 galactocele). Seven benign breast masses demonstrated focal radiotracer concentration at 10 minutes, of which 3 showed washout at 2 hours and 4 exhibited retention (3 inflammatory lesions and one tubular adenoma). All 24 malignant masses showed tracer concentration in the early (10 minute) phase. Uptake was focal in 21 and mild/ irregular in 3. Twenty malignant breast masses showed tracer retention upto 2 hours. Two breast lumps with early focal uptake and two with early irregular uptake showed washout of tracer in the delayed images. 3 out of these 4 masses were 2 cm or less in size, while only one was larger.

Discussions: Scintimammography using Tc99m sestamibi has a high sensitivity but relatively low specificity in the study of breast masses with suspicion of cancer [1]. Accumulation of this tracer depends on perfusion, viability and mitochondrial activity [2]. These factors may show significant overlap in some benign conditions and malignant tumors, and false positive tracer concentration has been reported in the early (10 minute) images in fibroadenoma, papilloma, abscess, granuloma and inflammation [3]. Using dual phase SMG, the specificity of late phase imaging at 2 hours has been found superior to early imaging alone [4], due to prolonged tracer retention by malignant breast masses.

In our study of 54 patients with breast lumps, all 24 malignant masses invariably showed tracer uptake at 10 minutes. Twenty one of the twenty four (87.5%) showed focal tracer uptake, with prolonged retention in 20/24 (83%). Nearly seventy seven percent of benign breast masses show mild or no tracer concentration in the early phase, with washout of tracer by 2 hours seen in 70% of the former group. Of the 7/30 benign masses (23%) with focal uptake in the 10 minute image, nearly half showed washout by 2 hours. Only 4 benign masses (13%) showed focal uptake with retention, of which 3 were inflammatory in nature. Thus, malignant breast masses tend to show focal concentration of Tc99m-sestamibi with retention upto 2 hours, while most benign masses exhibit either no uptake of the tracer or minimal, irregular uptake with washout by 2 hours.

Conclusions: Different patterns of Tc99m Sestamibi concentration in benign and malignant breast masses are described in this study (Fig. 1). These patterns may be used to characterize such masses, in correlation with other investigations in the diagnostic workup of breast lumps.

Fig 1. Dual phase scintimammography: patterns of Tc99m-sestamibi concentration in benign and malignant breast masses



Fibrocystic disease (No tracer uptake)

Infiltrating duct Ca (Focal uptake with retention)

Inflammation (Irregular uptake with retention)

Fibroadenosis (Focal uptake with washout)

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Incremental value of technetium MIBI SPECT, MR fusion imaging in evaluation of intracranial space occupying lesions

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Aim: Discriminating correct etiology of Intra Cranial Space Occupying Lesions (ICSOLs) detected by MRI is of great importance in deciding the right therapeutic approach. Our aim was to assess efficacy of Cerebral SPECT (CSPECT) in differentiating various etiologies (i.e. Infective / Inflammatory, Neoplastic & Post RT changes) of MRI detected ICSOLs. We also aim to determine the incremental value of quantitative uptake ratios in identifying exact nature of ICSOLs and to assess utility of Integrated SPECT/MR fusion images in enhancing the interpretative skill.

Materials & Method: 46 Pts (M: F = 31:15), age range 28 – 76 yrs, mean 42 ± 7 yrs were evaluated by ^{99m} Tc SestaMIBI CSPECT. 14/46 pts were HIV positive cases while remaining 32 were treated pts of intracerebral malignancies. All pts had one or more discrete MRI detected ICSOLs.

6/14 pts with HIV & 11/32 pts in the non HIV group showed more than 1 discrete ICSOL.

20 mCi of ^{99m} Tc SestaMIBI was injected IV. 15 min (early) & 2 hrs (delayed) post injection

CSPECT images were acquired on dualhead Gammacamera. Transverse, coronal and sagittal SPECT images were automatically or semi automatically aligned with MR images using common three-dimensional coordinates. All images were in DICOM format and alignment was performed using co-registration software.

Focal SestaMIBI uptake in MRI detected ICSOL was interpreted as abnormal. Uptake index (Ix) was calculated in early and delayed images as ratio of counts in lesion to that of contra lateral region. A value of > 1.3 was considered abnormal. Persistent Ix of > 1.3 in initial & delayed images were considered to be malignant while Ix of more or less than 1.3 in initial but less than 1.3 in delayed images was considered to be benign in both groups.

Results: In HIV group (14 pts), 4 pts showed Ix of < 1.3 in both early, delayed images & 7 pts showed an Ix of > 1.3 in early but significant washout of SestaMIBI in delayed images (Ix < 1.3). So 11/14 pts were diagnosed to have infective / inflammatory SOL (TB / toxoplasmosis) & were followed up for minimum 5 months. 10/11 pts improved / did not show any deterioration while 1 pt deteriorated (93% specificity). Remaining 3 pts who showed significant tracer uptake in both images (> 1.3 Ix) were diagnosed to have cerebral malignancy & underwent biopsy, proved to be positive for lymphoma (100% sensitivity, specificity).

In non HIV group (32pts), (i.e.tumour recurrence Vs Post Radiotherapy edema) 20/32 pts showed features of recurrence with a persistent Ix of > 2.0 & 12/32 pts showed two patterns of MIBI uptake a) 8/12 pts Early Ix of > 1.3 with significant washout of SestaMIBI in delayed images (Ix < 1.3) & b) 4/12 pts Early & Delayed Ix of < 1.3 prompting a diagnosis of post radiotherapy edema. 1 pt in benign group deteriorated & was diagnosed to have a recurrence. (Specificity 85.7%)

Discussion: Functional imaging with C SPECT is a useful tool to differentiate malignant from other benign cerebral pathologies. Uptake of MIBI is proportional to S phase cell cycle, aneuploidy, high-grade tumour. This differentiation can be further enhanced using Software fusion technology primarily based on volumetric techniques for image registration such as Mutual Information algorithm & other related methods. Results of SPECT imaging along with three-dimensional integrated display of SPECT, MR brain images indicate that combined use of these techniques provide a potentially

comprehensive diagnostic, functional information about ICSOLs in relation to brain anatomy and help in differentiating benign from malignant with more confidence.

Conclusion: C SPECT with MR fusion is a very useful tool in evaluating MRI detected ICSOLs both in HIV positive & follow up pts of treated intracranial malignancies. Our study shows a high degree of sensitivity and specificity of Tc-MIBI brain SPECT in identifying nature of lesions. An uptake index of 1.3 seems to be a good cut off value to determine malignancy while performing C SPECT. Integrated display of SPECT and MR brain images provides better localization of ICSOLs in relation to anatomy of brain than single-modality display and increases the confidence of observer.

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Tc99m DMSA -V Scintigraphy in post-operative follow-up of patients with medullary thyroid carcinoma

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Aim: Tc99m-V dimercaptosuccinic acid (DMSA) has been successfully used to image patients with medullary thyroid carcinoma (MTC). We performed this study to evaluate the role of Tc99m DMSA -V Scintigraphy in pos66

t-operative follow-up of patients with Medullary Thyroid Carcinoma.

Matierial Methods: We conducted a retrospective analysis of DMSA-V scans in 13 patients (7 M, 6 F with age range from 14 to 71 years) of MTC. Of these 13 patients, one had MEN II syndrome, two had phaeochromocytoma with MTC, and 10 had only MTC. Nine of the 10 MTC patients had undergone total thyroidectomy and 1 hemi-thyroidectomy. Histopathology confirmed the presence of MTC in all these 10 patients. Tc99m DMSA-V scan was performed post-operatively in all the 10 patients with MTC while in other 3 patients, scan was done pre-operatively also. During clinical follow-up, recurrence in thyroid bed was suspected in 1 and cervical lymph nodes metastases in 4. Serum calcitonin levels were measured for evaluation of tumor recurrence / metastases. Six of the ten post operative cases showed abnormally elevated serum calcitonin levels (range 304 pg/ml to 42,463 pg/ml, mean 6870 pg/ml). A standard scintigraphic protocol was followed in all patients. Whole body images in anterior and posterior views were acquired at 30 min and 2 hrs after i.v inj of 10 to 12 mCi of Tc99m DMSA-V.

Results: Tc99m DMSA-V scintigraphy showed radiotracer concentrating foci in 9 patients – 3 in the thyroid bed only, 1 in thyroid bed with distant metastasis, cervical lymph nodes in 3, and only distant metastasis in 2. One patient with phaeochromocytoma also showed uptake in adrenal gland suggesting recurrence.Four patients in whom there was clinical suspicion of local recurrence did not demonstrate elevation in serum calcitonin levels and in these patients there was no focus of abnormal DMSA-V avid lesion. The average serum calcitonin levels in three patients with local recurrence and distal metastasis on scintigraphy was 41,500 pg/ml. In the remaining six patients with local recurrence in thyroid bed or cervical lymphnodes the average serum calcitonin levels were 1,371 pg/ml. One patient of MEN II showed presence of parathyroid adenoma on Tc99m sestamibi imaging and metastasis in femur on Tc99m MDP bone scan. The focus of femoral metastasis was also evident on DMSA-V scintigraphy.

Discussion: The use of Tc99m DMSA-V scintigraphy in medullary thyroid carcinoma was first reported by a group of investigators from Japan [1]. The exact mechanism of localization of DMSA-V in MTC is not currently known. It is postulated that DMSA-V resembles phosphate ion and is taken up by tumours showing calcification like MTC and osteosarcoma [1]. DMSA-V has no well defined role in pre-operative staging of MTC [2]. Though initially developed as a non specific tumour imaging agent, DMSA-V has developed as an reliable scintigraphic tool in follow up of operated cases of MTC. The range of reported sensitivities in literatue for DMSA-V scintigraphy in detecting post operative MTC recurrences is from 50 to 80% [3-5]. In most of the scintigraphic protocols images are acquired at 2 to 3 hrs after intravenous injection of 10 mCi of Tc99m DMSA-V. It has the advantage of low cost, easy availability and high quality images; the use of SPECT may further improve the diagnostic sensitivity. Serum calcitonin is used as a serum marker for detecting recurrences in operated cases of MTC. In our study we found a high degree of co-relation between serum calcitonin levels and lesion detect ability on DMSA-V scintigraphy. The average serum calcitonin levels in patients with local recurrence and distant metastasis on scintigraphy was 41,500 pg/ml compared to 1,371 pg/ml in patients with local recurrence only. This probably is due to large tumour volume

bearing a positive co-relation with serum calcitonin levels and DMSA-V scan. Scintigraphy was useful in confirming recurrences/metastasis and directing futher therapy accordingly.

Conclusion: Elevated serum calcitonin levels is a well estblished sensitive marker for detecting recurrence / metastases in operated cases of medullary thyroid carcinoma. Greater levels of elevation in serum calcitonin are found in patients with distant metastasis. However it does not provide any information regarding the site of recurrence/metastasis. In this regard, Tc99m DMSA-V scan appears to be a reliable noninvasive localization technique during post –operative follow up of patients with MTC.

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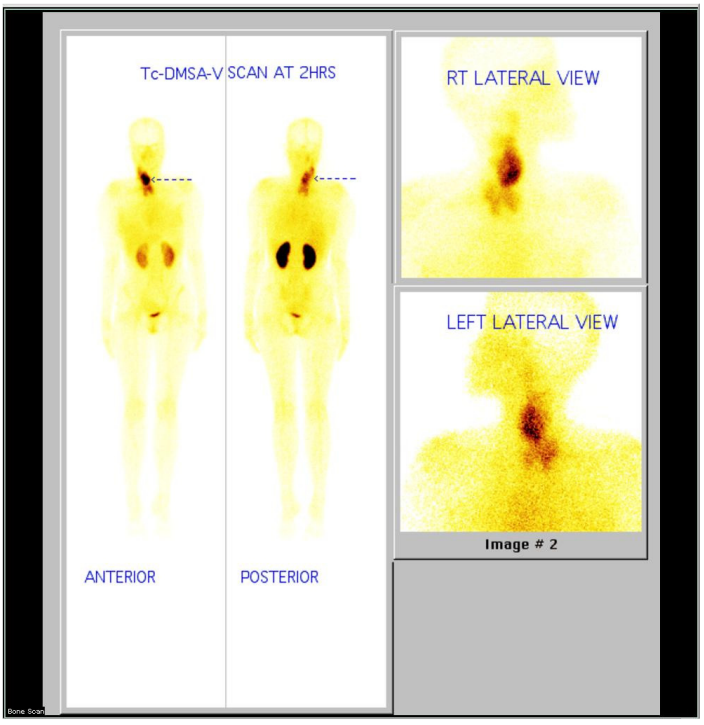

FIG. 1. This 36 years old female patient is a diagnosed case of medullary carcinoma of thryoid, status post total thyroidectomy and was on regular follow up. She presented this time with recurrent swelling in the right side of neck, and on further investigation was detected to have raised serum calcitonin levels (42623 pg/ml), normal thyroid hormone profile, and a 2x1.5 cm heterogenously enhancing lesion in the right carotid space on CT neck. Whole body and static images displayed above show a focus of DMSA V avid lesion in the right side of neck which was later confirmed by FNAC examination to be recurrent medullary thyroid carcinoma.

Usefulness of SPECT in sentinel node localisation

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Purpose: To describe the clinical usefulness of SPECT imaging in difficult sentinel node localisation, in several tumours.

Material and Methods: From December 2006 to February 2007, 142 patients were scheduled for sentinel node (SN) mapping (90 with breast cancer, 14 with malignant melanoma and seven with cervix uterine cancer). From these, seven patients had unclear or no visualization of the sentinel nodes in planar imaging, and SPECT images were performed to clarify localisation of the SN. The seven patients consisted in three with breast cancer, three with melanoma (one dorsal, one in the lumbar region and one in the posterior leg – a child age 6 years old) and one with cervix uterine neoplasia.

Scintigraphy was performed with a SPECT E-CAM gamma camera with a single detector, using a high resolution collimator, after injection of 148 MBq (4 mCi) of Tc-99m dextran in four equal aliquots of 0.4 mL each, which were injected at th borders of the primary tumour site with a 25-gauge insulin syringe. The dose for the pediatric patient was 37 MBq divided in four aliquots.

In melanoma and breast cancer patients injection was intradermal and in cervix uterine cancer, submucosal. Lymphoscintigraphy was performed one day before surgery. Planar images were obtained minutes after injection and continued until SN were identified. SPECT was performed with a matrix size of 128 x 128, 360°, 32 views, with a 20 second time frame.

SN identification was done by three of the authors, working independently and then jointly, to precisely localise the SN. The surgeon was notified in all cases and came to the Nuclear Medicine Center, to acknowledge the localisation. The patient was taken to the operating room the next day after lymphoscintigraphy. Skin marking was done and revised by a Nuclear Medicine specialist, immediately before surgery. A hand-held probe (Europrobe®) was used in the Nuclear Medicine department, for precise marking and other probe (Navigator®) was used in the operating room. A patent blue dye was injected in four points, at the borders of the primary tumour site, similar to the radiopharmaceutical injection.

Results: In six out of seven patients, SPECT added clinically relevant data. Table 1 summarizes scintigraphic and histopathologic findings of the patients.

TABLE 1. SCINTIGRAPHIC AND HISTOPATHOLOGIC FINDINGS IN SENTINEL NODE LOCALISATION

Pat	Age	Sex	Tumor type and location	Planar Imaging		SPECT Imaging		SN Histopa-thology
				First node detected	Clear localisation?	Addit. nodes	Relevant value	
1	39	F	Uterine cervix carcinoma	Obturator	No	One, interiliac	Additional SN	No mets
2	67	M	Dorsal malignant melanoma	Not detected	No	One	None	No nodes resected
3	69	F	Breast cancer	None	No	One	SN localized	No mets
4	6	M	Leg malignant melanoma	Inguinal	No	One, in transit	Wider resection	No mets
5	48	M	Lumbar malignant melanoma	Axillary	No	Two	Additional SN	No mets
6	57	F	Breast cancer	Axillary	No	One	Additional SN	No mets
7	67	F	Breast cancer	Axillary	No	One	Additional SN	Pending

Preoperative SPECT provided additional localisation of sentinel nodes in six patients, allowing a precise biopsy. Unpredicted sentinel nodes were found in melanoma patients and difficult location SN in breast cancer patients. The pediatric patient reported is the first one in which the lymphatic mapping has been done in this country. Possible explanation of additional detection is due to improved tomographic imaging technology. The patient with no detection neither in planar nor tomographic location remains a small percentage found in several series.

Conclusion: SPECT SN mapping adds relevant dat and should be done in difficult or unpredicted locations.

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^{99m}Tc-HYNIC-TATE receptor imaging and computed tomography (CT) in neuroendocrine tumour imaging

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Background: In neuroendocrine tumours (NET) workup it is often difficult not only to visualize but also to co-localize anatomically the lesions. The receptor scintigraphy allows to image the NETs with the receptor overexpression. NETs usually overexpres the subtype 2 of somatostatin receptors (SSTr). Therefore many somatostatin analogs like: ^{111}In-octreotide were used to visualize these tumors. The sensitivity of Somatostatin Receptor Scintigraphy (SRS) for NET is 70-90%.Behe and Maecke introduced hydrazinonicotinamide (HYNIC) as a bifunctional chelator for ^{99m}Tc labelling of octreotide and Tyr3-octreotide (TOC) with high efficiency (1). The ^{99m}Tc-HYNIC-TATE is the new preparation to the detection for NET. The Tyr3-octreotate (TATE) somatostatin analogue differs from TOC in that the terminal threonine replaces threoninol. The terminal threonine results in a higher receptor binding and better internalisation, with the consequence that tumour uptake of the tracer is intense [1].

Aim: The aim of the study was to assess the efficacy of the new ^{99m}Tc-HYNIC-TATE preparation in the NETs imaging with the overexpression of somatostatin receptors (SSTR).

Methods and material: The ^{99m}Tc-HYNIC-TATE preaparation produced by OBRI POLATOM (Poland) was used to assess 81 patients with clinical, patological or laboratory proof for neuroendocrine tumour. The scintigraphy was acquired on the double –head gamma camera in 10 min, 2-3 h and 24 h after intravenous injection of ^{99m}Tc-HYNIC-TATE. The injected activity was 550-740 MBq (15-20mCi). The following views were gathered: planar AP, PA and SPECT of the head, chest and abdomen. All patients were scanned (chest and abdomen) routinely with 16-row CT. The image processing and fusion was performed on the dedicated workstation Hermes Nuclear Diagnostic (Sweden).

Results: ^{99m}Tc-HYNIC-TATE confirmed the presence of NET in 66 patients. In 10 patients the thyroid cancer was found and in 5 subjects the acromegaly was diagnosed. The fused images of receptor imaging and CT allowed to precisely localize the pathological tracer uptake and to detect the tumour in 83% patients.

Discussion: Endocrine tumours are heterogeneous group of neoplasms. ^{111}In-Octreoscan has been the "gold standard" in the imaging diagnosis of endocrine tumors. ^{99m}Tc-EDDA/HYNIC-octreotate scans showed similar physiological biodistribution of the tracer in comparison to ^{111}In-Octreoscan SRS. In vitro studies with somatostatin receptors revealed that TATE, shows 14- to 17-fold higher affinity for SSR2 than octreotide and eight- to tenfold higher affinity than TOC [2]. ^{99m}Tc-EDDA/HYNIC-octreotate whole body scans revealed more metastatic lesions, with higher target/non-target count ratios [3]. In comparison to CT, ^{99m}Tc-EDDA/HYNIC-octreotate appeared to be a more sensitive modality in the detection of the primary lesions and liver and abdominal lymph node metastases [4]. The development of image fusion SRS and CT or MRI will significantly improve the early localization of carcinoids. In our study ^{99m}Tc-EDDA/HYNIC-octreotate had a high accuracy for detection of the endocrine tumors. Fusion imaging SPECT and CT scans in diagnosis of the endocrine tumours enables both pathological and physiological changes to be localized precisely.

Conclusion: The ^{99m}Tc-HYNIC-TATE preparation is useful in NET imaging. The image fusion with the CT data enables to precisely co-localize the lesions with pathological uptake.

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Myocardial perfusion gated SPECT in women with positive stress test

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Background: Coronary artery disease is the leading cause of morbidity and mortality in industrialized societies. Modern diagnostic strategy in coronary artery disease (CAD) requires not only to establish the diagnosis but also to assess the cardiovascular risk [1,2]. It is not certain how to manage women with ST changes during stress test [3]. It is not clear what scintigraphic findings should warrant coronary angiography in those subjects.

Aim: The aim of the study was to assess the prognostic value of myocardial perfusion scintigraphy and coronary angiography in women with ST changes during ECG stress test.

Methods and material: The study population consisted of 171 women with ST changes during stress test. Group I consisted of 115 females who were subjected to myocardial perfusion scintigraphy as the first step in the sequential diagnostic procedure, in 58 of them the coronary angiography was also performed. Group II included 56 women in whom coronary angiography was done directly after the positive ECG stress test. The gated single photon emission computed tomography (GSPECT) with Tc-99m MIBI was considered positive if the moderate perfusion changes were noted in at least 2 segments or severe perfusion deficit was found. In all women from group II and in 58 subjects from group I the coronary angiography was done. The degree of stenosis was assessed visually and 50% of lumen stenosis was considered haemodynamically significant.

Results: The follow-up was concluded after 36.52±27.54 months. The sensitivity of myocardial perfusion scintigraphy was 82.4% against coronary angiography and 100% against the cardiovascular event. The specificity was 85.5% and 93.1% respectively. The positive predicitive value of coronary angiography for cardiovascular event was 70.6% and 62.5% for the group I and II respectively. The percent of negative results of coronary angiography was significantly lower in the group were sequential diagnostic was provided (group I) comparing to the group were cardiac catheterization was performed directly (group II). However both groups didn't differ statisticaly in terms of future cardiac events. The survival analysis showed high prognostic value of the SPECT and coronary angiography. However if compared the SPECT was better than coronary angiography ($Chi^2=9.39$, $p<0.01$).

Discussion: The high prognostic value of myocardial perfusion scintigraphy was demonstrated in a number of studies [4]. There are data suggesting that an abnormal SPECT test confers a higher risk of cardiac death or myocadial infarction for women than men [5]. A recent meta-analysis of Metz et al. [7] showed that exercise myocardial perfusion imaging have high negative predictive value for primary and secondary cardiac events and that the prognostic utility of this modality is similar for both men and women. However so far only few studies examined the prognostic value of myocardial perfusion scintigraphy in patients with suspected CAD, not proven by coronary angiography [6]. In our study myocardial perfusion scintigraphy had a high diagnostic and prognostic value in the cohort of women with suspected CAD. The normal scan guarranted low event rate for women with haemodynamically significant lumen stenosis.

Cardiac catheterization is the gold standard diagnostic test for establishing the presence of CAD. However in the WISE study [8] it was shown that among women referred for catheterization, approximately 50% did not have significant angiographic disease, and the prognosis for these women was not benign in terms of future adverse cardiac events and persistent symptoms. The high prognostic

value of coronary angiography shown in our study could be subsequent to the fact that most of the end-points were revascularization procedures. Nevertheless our study showed that performing myocardial perfusion scintigraphy after the positive ECG stress test as the next step in sequential diagnostic of CAD in women can diminish the percent of unnecessary invasive tests by 15%. The similar findings had the END study invastigators [9].

The prognostic value of myocardial perfusion scintigraphy was not fully compared to the value of coronary angiography in the population of women with suspected CAD and positive ECG stress test. In our study it was shown that in women with suspected CAD and positive stress test, SPECT was better than coronary angiography in predicting future cardiac events. Although some previous studies [10,11] proved that SPECT had higher prognostic value than coronary angiography in patients suspected of CAD, however the gender related differences were not assessed.

Conclusion: The myocardial perfusion scintigraphy in females with ST changes during ECG stress test is a powerful predictor of outcome and may enhance the positive predictive value of coronary angiography.

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Assessment of cardiovascular system in subclinical hyperthyroidosis

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Background: Subclinical hyperthyreosis (SH_{yper}) affects about 1,5% population and may be responsible for many non specific symptoms. Consistent evidence indicates that subclinical hyperthyroidism reduces the quality of life, affecting both the psycho and somatic components of well-being, and produces relevant signs and symptoms of excessive thyroid hormone action, often mimicking adrenergic overactivity [1]. Therefore the diagnosis of this disease leans on the laboratory criteria only: decreased of TSH and normal FT3 and FT4 levels found in the same time. The endogenic form, which is the effect of excess of thyroid autonomic tissue may lead to overt hyperthyreosis. It often causes the adverse infuence on mental and somatic health and quality of life. Moreover it increases mortality and there is no unequivocal procedure algorithm how to manage patients with SH_{yper}.

Aim: to estimate an influence of SH_{yper} on cardiovascular system (CVS), to find the relationships between parameters of CVS dysfunction and SHyper severity, to establish which diagnostic method is useful to make a decision to start a treatment. Morever the objective was to The aim of the study was to to investigate the presence and reversibility of cardiac abnormalities in poststress gated SPECT in patients with long-term endogenous subclinical hyperthyroidism.

Method: 44 patients (37 women and 7 men) aged 45,9 ± 11, with 12,8 ± 9,8 month history of endogenic SH_{yper}, were examined twice: before and 5,7 ± 4,2 months after TSH normalization with radioiodine treatment with the use of five CVS diagnostic methods: 24 hour - 12 lead - Holter electrocardiography with heart rate variability evaluation, ambulatory blood pressure monitoring, treadmill exercise electrocardiography, radionuclide ^{99m}Tc - MIBI – GSPECT scans and echocardiography. The average time between examinations was 12,5 ± 6 months.

Results: The exercise tolerance improved in the 84% of patients despite the cardiac output decreased from 3.97+/- 1.2 to 3.75 +/-1,3 l/min, P=NS. There were no statistical differences in global and regional perfusion before and after treatment on summed images. In 12 patients after the treatment we observed the improved perfusion on end–diastolic images. The group with end-diastolic perfusion changes had a higher FT4 and FT3 ($p<0.05$). The time to reach the normal TSH value was different: 5,9 and 9,2 months ($p<0.05$) for the group without and with changes respectively. In this low cardiovascular risk population the systolic function mean left ventricluar ejection fraction = 64 +/- 12 at baseline did not change significantly. Poststress cardiac output decreased from 3.97+/- 1.2 to 3.75 +/-1,3 l/min, P=NS. The significant improvement was seen in time to peak filling rate (changed from 175 +/- 85 to 151 +/- 69 ms, $P<0.05$). The improvement in peak filling rate was not statistically signficant.

Discussion: Our findings prove th diagnostic role of gated SPECT in the diagnostic workup of patients with subclinical hyperthyroidism. Together wioth other cardiovascular test ir may soon serve as the decision making tool, whether to treat patients with SH_{yper}. The major cardiovascular findings in patients with SH coupled with undetectable TSH are a higher heart rate and a higher risk of supraventricular arrhythmias [2-4]. The most consistent cardiac abnormality is a significant increase in left ventricular mass with unchanged or increased at-rest systolic function and, usually, impaired diastolic function [5-7]. Moreover, reduced systolic performance on effort and decreased exercise tolerance has been reported in patients with SH who had a greater increase in left ventricular mass [8].

Thyroid hormone-induced hypertrophy in SH is due primarily to the cardiac response induced by the increased cardiac workload. This is accordance with cardiac hypertrophy induced in rats by thyroid hormone excess [9]. Moreover, the significant increase in left ventricular mass with a tendency towards LV concentric remodelling reported in patients with long-standing SH [3,6,7] may counteract the favourable effect acutely exerted by thyroid hormone on diastolic performance, and so lead to impaired ventricular relaxation and systolic dysfunction during effort. The altered passive elasticity of the ventricle (chamber stiffness) determined by the presence of myocardial hypertrophy is the major determinant of diastolic dysfunction in patients with subclinical hyperthyroidism. However, the increase in heart rate and in left ventricular mass usually precedes the onset of more severe cardiovascular disease, and is an independent risk factor for increased cardiovascular morbidity and mortality in the general population.

Conclusion: It was found that excess of thyroid hormones during endogenic subclinical hyperhyreosis affects cardiovascular system on several levels:on the tissue level as: increase of aortic diameter and volume of heart cavities, increase of left ventricular mass with diastolic dysfunction and myocardial electrical instability,on the cardiovascular system level as: increase of heart load, increase of blood pressure in night time, decrease of activity of parasympathetic nervous system, generally - as decrease of maximal exercise capacity. Gated SPECT may detect the left ventricular volume changes and end-diastolic perfusion/function abnormalities in patients with subclinical hyperthyroidism.

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Myocardial perfusion imaging - A possible role in revealing endothelial dysfunction in patients with angina and normal coronary angiogram

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Aim/Background: A lot of recent studies have shown that patients with normal or nonobstructive coronary angiography have myocardial ischemia; the pathogenesis in this particular case is related with endothelial dysfunction which contributes to the initiation and progression of atherosclerotic disease and could be considered an independent vascular risk factor. Endothelial status is not determined solely by the individual risk factor burden but rather, may be regarded as an integrated index of all atherogenic and atheroprotective factors present in an individual, including known as yet-unknown variables and genetic predisposition. The aim of our study was to evaluate perfusion defects on stress myocardial perfusion single photon emission computed tomography (SPECT) in patients with chest pain and normal angiograms and their prognostic values.

Materials and Methods: We studied 32 patients who underwent stress (treadmill exercise test)/rest SPECT and coronary angiography; all the patients had at least two risk factors for atherosclerosis; they were followed up during 36 months for the occurrence of myocardial infarction, revascularization or cardiac death. A semiquantitative scoring method was used to evaluate technetium-99m tetrofosmin uptake in 20 myocardial segments in each patients. Each segment was assessed by consensus of two nuclear medicine physicians who were blinded to the clinical and angiographic information. For each segment a 5-point scoring system was used to describe radiotracer uptake (0=normal, 1=equivocal, 2=moderate, 3=severe reduction, 4=absence of detectable radiotracer in a segment). SPECT results were categorized as normal or abnormal if <3 or >/=3 segments, respectively were affected.

Results: 9 patients showed myocardial perfusion defects (SPECT positive group); the others 23 did not show myocardial perfusion defects (SPECT negative group). During the follow-up in the SPECT-positive group 1 patients developed acute myocardial infarction and 3 patients underwent coronary revascularization due to severe stenosis. In the SPECT negative group only 1 patient underwent revascularization.

Discussion: In the SPECT-positive group 4 from 9 patients (44%) have significant cardiovascular events during the follow –up in comparison with 1 from 23 patients (4.3%) in the SPECT-negative group. Even if the results were obtained from a sample of highly selected patients referred for coronary angiography to evaluate persistent chest pain, they proved that stress SPECT-myocardial perfusion imaging was able to detect the early stage of atherosclerosis.

Conclusion: In patients with angiographically normal-appearing coronary arteries, the presence of myocardial perfusion defects could be an expression of atherosclerotic-related endothelial dysfunction; the detection of ischemia has a great clinical value in identifying patients at high risk of subsequent coronary events; so, in this group of patients, aggressive medical therapy, risk factor management and lifestyle changes should be considered. On the other hand, SPECT imaging should be evaluated as a noninvasive method of revealing endothelial dysfunction in the departments without a PET equipment.

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Value of 99mTc-MIBI brain SPECT in differentiating recurrence and radiotherapy effects in tumors brain patients

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Accurate neuroimaging can assist in the diagnosis, management, prognosis, and follow-up of central nervous system (CNS) malignancie. Differentiation between tumor progression and radiation necrosis is one of the most difficult tasks in oncologic neuroradiology. The main role of functional imaging in oncological practice is to determine whether a lesion observed in an anatomical study such as CT scan or MRI consists of tumor cells or is formed by fibrotic tissue only. 99mTc-MIBI brain SPECT is considered a useful tool in the management of brain tumors. The demonstration of increased tracer extraction and subsequent accumulation in the lesion indicates viability of the suspected tumor mass.

Aim: Gliomas, arising from glial cells, account for approximately the 45-55% of all brain tumors. 99mTc-MIBI tumor uptake is related to histological grading, cellular proliferation index and prognosis. Our aim was to evaluate 99mTc-MIBI brain SPECT and MRI studies efficacy in the differential diagnosis between recurrence of malignant gliomas and glioblastomas and the local modification after radiotherapy.

Material and methods: Eight patients with suspected recurrence after surgical removal of a supratentorial glioma (2 low grade and 6 high grade), 6-12 months before study and treated with radiotherapy were investigated. For brain SPECT – 740MBq of 99mTc-MIBI were i.v. injected to each patient 15 minutes before image acquisition by a dual-head gamma camera, using a fan-beam collimator. Transverse, coronal and sagittal views were reconstructed. Gd-DTPA enhanced T1 and T2 weighted MRI studies were carried out in every patient within 3 days before 99mTc-MIBI SPECT. The brain SPECT images were analyzed by calculating lesion-to-normal ratios (l/n). Areas of abnormal tracer uptake were defined as focally increased uptake or as asymmetric uptake, compared with the contralateral side. Uptake ratios were calculated using reference regions in the contralateral hemisphere, because of the limitations of SPECT in providing absolute quantification. Regions of interest (ROIs) were delineated on the 2 transaxial slices with the highest tracer uptake in the lesion. The ratio between the tumor ROI on a slice with maximum uptake and a mirrored control ROI was calculated and if >2 it was considered pathological.

Results: The results of MRI and 99mTc-MIBI brain SPECT studies were matched and analyzed. Both studies well correlated being both positive for recurrence in 5 patients as confirmed by biopsy (biopsy was performed when re-operation was judged safe and useful), while both negative in 2 patients, considered as having radiation effects (evaluate by clinical follow up). One patient with negative SPECT was operated being severely symptomatic and the biopsy was positive for low grade tumor. Combined sensitivity was 83,3%, specifity 100%, NPV 66% and PPV 100%.

Discution: Treatment efficacy in malignant glioma is evaluated by neuroimaging studies. Conventional MRI assess morphologic parameters such as changes in tumor size and contrast enhancement. However, changes in size and alterations in blood–brain barrier properties (after therapy) not only reflect therapeutic efficacy but also can represent nonspecific inflammatory reactions due to irradiation, tumor necrosis, or postoperative enhancement along the resection margins. ^{99m}Tc-MIBI concentrates in mitochondria by active diffusion because of an increased negative transmembrane potential. Because there is no reason for MIBI uptake in nonvital tissues, ^{99m}Tc-MIBI brain SPECT can be used to evaluate tumor viability and therapeutic response in malignant glioma patients. According to our results, the specificity and sensitivity of ^{99m}Tc-MIBI brain SPECT and MRI studies in detection of

relapses of gliomas and glioblastomas seem to be high and also the most adequate anatomic depiction of extent of tumor process.

Conclusion: Our results confirm that MIBI SPECT is could be considered as a valuable tool to permit effective adaptation of the therapeutic regimen in patients treated for recurrent glioma. Clinical follow up of these patients is underway to assess correlation of metabolic response to clinical response.

Keywords: brain SPECT - MIBI - radiation necrosis - tumor recurrence

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SPECT radioimmunodetection of colorectal carcinomas using ^{111}In labelled monoclonal antibodies

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The aim of the study was evaluation of the accuracy and clinical impact of the single-photon emission computed tomography (SPECT) with ^{111}In labelled antibodies for the detection of metastases and recurrences of colorectal carcinomas.

Selection of patients was based upon complete diagnostic records (anamnestic data, physical examination, blood analysis, ultrasonography, contrast radiography, rectoscopy/ colonoscopy, computed tomography, magnetic resonance imaging, tumor marker essay), and a clinical follow-up of at least 6 months. The study was performed in 8 patients with INDIMACIS 19-9 containing 150 MBq of ^{111}In labeled MoAb 19-9 F (ab')2) and in 18 patients with ONCOSCINT CR 103, containing 150 MBq ^{111}In labeled B72.3 MoAb). Whole body scintigraphy was performed with ROTA scintillation camera immediately after application of radiopharmaceutical, as well as after 24h, 48h and, if necessary 72h using appropriate collimators (for medium energies), as well as energy settings (172 keV and 247 keV). SPECT ($360^o/6^o$) of abdomen and pelvis was performed after 24h-48h. Reconstruction was performed using Butterworth filter (6, 0.25).

With INDIMACIS 19-9, 8 patients were investigated (5 with colon and 3 with rectal adenocarcinoma), 8 months till three years after surgery. Two patients were investigated twice- second time after 3 months after surgery. Before surgery, one patient with rectal carcinoma underwent radiotherapy, while two underwent therapy after surgery. Three patients had chemotherapy after surgery.

With ONCOSCINT, 18 patients were examined (17 with adenocarcinomas of caecum, colon and rectum and one with squamocellulare colon carcinoma) from 4 months till two years after surgery. Two of them with rectal adenocarcinoma, underwent radiotherapy two months before our investigation. Four of the patients had chemotherapy after surgery.

With INDIMACIS 19-9, there were 2/8 TN, with borderline value of CEA and Ca 19-9. TP were 6/8 (all with elevated tumor marker values, four of them many times; 3 with recurrences, 1 with recurrence and liver metastases and two with only liver metastases). In two patients with proved liver metastases in whom the study was repeated after 4 i.e 6 months after surgery, tumor marker values were mildly elevated, and liver metastases were confirmed again (in one patient US, CT and MRI were negative). Recurrences were 4-6 cm and liver metastases from 18 to 45 mm. In three patients with only recurrences, only SPECT was positive. In one patient without recurrences, CT finding and colonoscopy were false positive (postradiation scar tissue), while immunoscintigraphy/SPECT finding was true negative. In the other patient with recurrence, CT finding, contrast radiography and rectoscopy/colonoscopy proved a mass due to postradiation necrosis while immunoscintigraphy/SPECT finding was positive. In all the patients with liver metastases, immunoscintigraphy was positive, while other diagnostic methods (MRI, CT, US) were negative in one. Thus, in three patiens, immunoscintigraphy/SPECT results influenced patient further management.

With ONCOSCINT, in 9 patients recurrences of carcinomas (5-12 cm), in one patient recurence with peritoneal carcinosis, in 2 recurrences with liver metastasis, and in two only liver metastases were

detected by immunoscintigraphy and confirmed by surgery (TP=14/18). Only SPECT finding was positive in 5 patients with recurrences. In 2 patients findings were TN, in one FN (false negative) and in one FP (false positive). FN finding was in one patient with recurrence smaller than 1.5 cm, subsequently proved by colonoscopy. FP finding was in one patient with granuloma.US and CT/MRI were positive in all patients with liver metastases, CT finding was false negative in two patients with recurrences, while MRI in one. In three patients with recurrences, CEA blood level was not increased. In 4 patients intensive accumulation of labelled antibodies was observed in colostomas. Also, immunoscintigraphy/SPECT was positive in one patient with squamocellulare carcinoma. Contrast radiography and rectoscopy/colonoscopy were TP in 13/16 patients with recurrences. In one, both methods were negative because of the extraluminal tumor localization, and in two patients, both methods were impossible to perform (patient with colostoma, and postoperative scar strictures). In 5 patients, immunoscintigraphy/SPECT influenced the management of the patients.

Immunoscintigraphy significantly influenced the management of 38% and 28% of the patients. The true application of this method should be detection of recurrence, assessment of viability as well as follow up of the therapy.It is particularly important in the cases when other methods have limitations: CT and MRI viability assesment after surgery, radio and chemotherapy, and contrast radiography and colonoscopy dificulties to be performed.Disadvantages of immunoscintigrapphy are lower resolution, low target/background ratio and nonspecific uptake of the radiopharmaceutical in organs and tissues. With SPECT, better distinction of tumour in comparison to other structures and estimation of its size is achieved, thus increasing the sensitivity of the method. Other imaging methods (CT,US,MRI) have advantage in detection of liver metastases, while immunoscintigraphy is more specific for the assessment of reccurences of the abdominal tumours. Thus immunoscintigraphy should be applied in patients with suggested local recurrences and inconclusive outcome of routine diagnostic workup.

Detection of neuroendocrine tumors using ^{99m}Tc-tektrotyd

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Aim/Background: ^{99m}Tc-Tektrotyd is a radiopharmaceutical indicated for diagnosis of tumors with overexpression of somatostatin receptors (especially subtype 2, $sstr_2$), which can be imaged with this radiolabelled ligand. The aim of the study is detection of primary and metastatic neuroendocrine tumors with whole body scintigraphy and SPECT.

Methods and materials: The total of 33 patients (13 males and 20 females, age 53±14 years) with different neuroendocrine tumours were investigated. Scintigraphy of the whole body was performed 2h, (if necessary 10 min and 24h) after i.v. administration of 740MBq ^{99m}Tc-Tektrotyd. In cases of unclear findings obtained by whole body scintigraphy, investigation was followed by SPECT. It was performed using 360^o orbit, step and shoot mode, at 30 sec per view. The acquired data were collected in a 128x128 computer matrix and reconstructed using filtered back-projections with a Butterworth filter (cut-off 0.6 cycles/pixel, oreder 5) and iterative reconstruction. If necessary, the study was supplemented with liver/spleen radiocolloid and/or bone diphosphonate scintigraphy. Before the study therapy with somatostatin analogues was withdrawn, mild laxatives were introduced, patients were fasting and were well hydrated. The study was performed with ECAM gamma camera and computer, using high resolution collimator and one photopeak activity (140keV±20%).

Results: In the group of nine patients with neuroendocrine tumors of unknown origin, there were seven true positive (TP), and two false negative findings (FN). Diagnosis was made according to SPECT findings in six patients of this group. In the group of eight patients with gut carcinoids, there were 4 TP, two true negative (TN), one FN, and one false positive (FP) finding. Diagnosis was made according to SPECT findings in two patients of this group. In the group of seven patients with neuroendocrine pancreatic carcinomas there were 4 TP, and 3 TN findings. Diagnosis was made according to SPECT findings in two patients of this group. In the group of six patients with lung carcinoids there were 4 TP, one TN, and one FN. Diagnosis was made according to SPECT findings in two patients of the group. In the group of three patients with gastrinomas there were 2 TP findings, and one TN. Diagnosis was made according to SPECT findings in two patients of the group. According to our results, overall sensitivity of the method is 84%, specificity 88%, positive predictive value 95%, negative predictive value 64% and accuracy 85%.

Discussion: Out of patients with neuroendocrine tumors of unknown origin, TP findings were obtained in four cases with liver metastases, three with lung metastases, two with bone metastases and one with mediastinal gland metastases. FN findings were obtained in one patient with liver metastases of the poorly differentiated tumor, and in another one with small lung metastases (< 1 cm). Out of patients with gut carcinoid, three of four with TP findings had liver metastases, two patients following surgery had TN findings, there was FN finding in one with small lung metastasis, and FP finding in one, probably caused by physiological activity accumulated in the bowel. Out of patients with neuroendocrine pancreatic carcinomas, TP findings were related to three casses with liver metastases and one with metastases in paraaortal lymph nodes, while TN findings included one patient with somatostatinoma, one with insulinoma and one with carcinoid after surgery. Out of patients with lung carcinoids, there were TP findings in two with liver, one with lung, and one with bone metsastases, while TN finding was related to one patient following surgery, and FN finding to one patient with poorly differentiated tumor. As far as patients with gastrinomas are concerned, in two patients there were TP findings (jejunal, pancreatic), and in one TN finding (paraduodenal). Out of 33 patients studied, SPECT contributed to accurate diagnosis in 14 (42%), including six patients with

neuroendocrine tumors of unknown origin, two with gut carcinoid, two with neuroendocrine pancreatic carcinomas, two with lung carcinoid, and two with gastrinomas. Also, this imaging method was useful for the further management of 15 (45,5%) patients, including four patients with neuroendocrine tumors of unknown origin, four patients with gut carcinoid, three with neuroendocrine pancreatic carcinomas, two with lung carcinoids, and two with gastrinomas. Finaly, radionuclide therapy with ^{90}Y-DOTA TATE had been indicated in 10, and already performed in five patients.

Conclusions: Our preliminary results show that scintigraphy of neuroendocrine tumors with 99mTc-Tektrotyd is a useful method for diagnosis, staging and follow up of the patients suspected to have neuroendocrine tumors. SPECT has important role in diagnosis. It is also helpful in the appropriate choice and monitoring of the therapy, including the radionuclide one.

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Molecular nuclear medicine in the management of thyroid cancer

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Background: SERUM thyroglobulin (Tg) is an established tumor marker used in the management of patients with a diagnosis of differentiated thyroid carcinoma (DTC) [1,2]. However, a number of technical problems impair the clinical utility of this test. These problems include a lack of method standardization, inadequate sensitivity, lack of interassay reproducibility, "hook" effects when measuring high concentrations, and Tg autoantibody (TgAb) interference [3]. Recently, progress has been made in overcoming some of these limitations. For example, a collaborative effort has now produced an international Tg standard (CRM 457, BCR Brussels) [4,5]. RIAs are being replaced by more sensitive immunometric assay (IMA) methods with faster turn-around times, and recommendations for improving interassay precision and detecting hook effects have recently been published [3].

The present study was carried out to evaluate the accuracy of recombinant human TSH (rhTSH) /thyroglobulin (Tg) test among differentiated thyroid cancer (DTC) patients with persistent disease and low thyroglobulin levels.

Methods and materials: Concentration of TSH and Tg was investigated using RIA. A series of 13 DTC patients was selected because they had proven persistent disease associated with low Tg levels (< 2.0 micro g/l) under l-thyroxine treatment. In all of them, serum Tg was > 5.0 micro g/l at the last THST withdrawal. We measured serum Tg and TSH levels on days 0.5, 1, 1.5, 2, 4, 7, 10 and 15 after the first of a 2-day course of intramuscular rhTSH injections. Serum Tg values were variable in terms of both peak and time-course.

Results: Detectable serum Tg levels were recorded on day 4 in all patients. However, among these 13 patients, the peak Tg value was reached earlier than day 4 in three patients and later in two others. In one patient, Tg level at day 2 was higher (3.0 micro g/l) than at day 4 (1.8 micro g/l). In six of the 13 patients studied we compared Tg values after rhTSH to those subsequently obtained after THST withdrawal: in five of them Tg values were two to three times higher after the latter stimulation. Serum Tg value variability after rhTSH was partially accounted for by variability of serum TSH levels, which were inversely related to patient body surface.

Conclusion: In DTC patients with persistent disease and low Tg levels, optimization of the diagnostic use of Tg measurement after rhTSH may require rhTSH dose adjustment to the patient body surface area and repeated blood sampling, in order to improve diagnostic accuracy. In these patients not even a TSH-stimulated serum Tg cut-off of 2.0 micro g/l on day 4 provides 100% accuracy, whereas a cut-off of 1.0 micro g/l seems more appropriate. Therefore, in this subset of patients, if any detectable Tg level >or= 1.0 micro g/l is found after rhTSH, re-evaluation after THST should be advised.

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Treatement of painful bony metastasis of prostatic cancer by Samarium 153 (Quadramet®)

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SUMMARY

Introduction: Despite of the progress realized in the treatment of prostatic cancer, the appearance of bony metastasis had limited considerably the life expectancy. In that case, pain is the most important symptom to consider because of its most frequency and the most difficult to manage. Its management needs a multidisciplinary approach with the objective of improving patients' life quality.

Aim: The objective of the study was to evaluate the interest of metabolic radiotherapy to ^{153}***Samarium-EDTMP,*** for the pain treatment of bony metastasis of prostatic cancer.

Material and method: This was a multicentric study where data were collected retrospectively lasting 40 months. The study was conducted in three departments of nuclear medicine: Institute Salah Azaiez, the center 'CERU', and military hospital of Tunis. Forty five patients with painful bony metastasis of prostatic cancer had been enrolled in the study. Efficacy and factors influencing treatment response had been assessed as well as toxicity and the cause of failures.

Results: Positive response was obtained in 92.1% of cases and response was completed in 36.5% of cases.

Results obtained after multiple administrations of treatment, showed that the cures could be repeated and could have results comparable to the first cure.

The efficacy of our treatment is at least equivalent to the one obtained by the other methods of treatment, with very rare adverse events.

The only toxicity was a hematological disorder that is usually moderated and reversible as well with complete recovery in around 8 weeks.

Conclusion: Our results supported the efficacy of 'Samarium153-EDTMP' in the management of painful bony metastasis of prostatic cancer.

Key words: Cancer, Prostate, Bony metastasis, Pain, metabolic radiotherapy, Samarium 153.

POSTER SESSION III

RADIOPHARMACY

Multi-tracer syntheses at a radiopharmaceutical production centre "A shift of paradigm"

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The positron emission tomography (PET) is an unique, non-invasive, powerful diagnostic tool at the forefront of modern functional imaging in clinical nuclear medicine. Traditionally PET is based on short-lived positron emitters (^{11}C, ^{13}N, ^{15}O, ^{18}F) which are produced by low-energy cyclotrons. Due to the short half-live fast technical and chemical processes are essential for the production and the synthesis of the radiopharmaceuticals. Since not every PET center can afford to have an own production cyclotron the availability of the different PET tracers at the wide spread PET centers is limited. Furthermore, PET is widely established as a routine assessment of cancer, neurological disorders as well as coronary artery disease in humans and the diagnostic fields are rapidly growing with the development and demand of new bio tracers.

At this point PET radiopharmaceutical production and distribution companies can serve such PET centers. The radionuclide ^{18}F is suitable for long-distance distribution. The half-live of 109 min, fast synthesis times and high yields allow transportation of multiple dose vials over a 6 hours time range. This gives the possibility to operate cyclotron centers on a commercial base and distribute PET radiopharmaceuticals to hospitals and private doctors over a certain distance. In consequence, commercial radiopharmaceutical production centers are challenged to offer an high product diversity at high yield production and quality levels. Also highly optimised logistics are necessary to build up a satellite distribution system to cover the amount of activity needed for applications in PET centres away from the production site.

In the present work an overview of the installation and the routine operation of ARGOS cyclotron and IASON Graz, two companies dedicated to the production and distribution of PET radiopharmaceuticals for the European market is given. It will reflect the problems of the daily production (e.g. coordination of the ordered doses, radiation dose to workers, multiple tracer production, etc.) and the logistical efforts (e.g. drivers, air planes, etc.). Furthermore, technical solutions are described which allow simultaneous high scale multi tracer productions under GMP condition in a clean room environment.

The company IASON is one of the leading PET radiopharmaceutical suppliers in Europe with two production sites in Austria (Klagenfurt, Linz) and one in Italy (Roma). Based on these cyclotron centres European countries, especially Italy and France, but also Germany and eastern European countries are delivered by car or aircrafts on a daily base. All three production sites are equipped with similar instrumentation. The radioisotopes are produced with GE PETtrace cyclotrons (dual particles in Klagenfurt and Linz) and a GE MINItrace in Roma. The cyclotrons are capable to run dual beam mode, so several hundreds GBqs of radioactivity can be produced in a short time followed by simultaneous syntheses of different tracers. The major product is EFDEGE® - 2-[^{18}F]fluoro-2-desoxy-D-glucose ([^{18}F]FDG) with an European registration in 16 countries.

Beside the routine production ARGOS has also an application oriented but strong R&D program focused on the development of radiopharmaceutical production sequences, targetry and the design of tracer production modules. In course of this program a modular tracer production system has been developed based on a disposable kit synthesis module which has been modified to a multipurpose synthesizer, and a system of separated product flows excluding cross-contaminations. To perform a HPLC-purification an interface module has been constructed containing product loading systems and all radioactive components controlled by a labview program. This system allows several simultaneous production runs of 10 different PET- tracer per day under GMP-conditions.

Transport of radioactive materials of short half-life

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Background: It is well known the importance of Positron Emission Tomography (PET) in diagnosis of heart diseases and oncology. In Brazil, the production of fluorine-18 (^{18}F) is performed in São Paulo and in Rio de Janeiro. ^{18}F is a radionuclide with a half life of less than one hour which requires an efficient and prompt transport infrastructure from the point where it is produced to the place where it will be used. This may be a problem in big cities like São Paulo and Rio de Janeiro where heavy traffic is a daily experience.

To fulfill the growing demand for ^{18}F it would be necessary to have an adequate number of cyclotrons machines providing this radionuclide where and when it is necessary [1]. However, due to their high costs, cyclotrons seem to be a long term solution. Consequently, there is a need for an immediate solution. In this connection, carriers have exercised a number of alternatives as, for example, a dedicated transportation team and the identification and use of optimal routes. These alternatives have demonstrated satisfactory results but represent higher costs.

Method and Materials: Observations of the experience in transport of other goods have provided an indication of possible solutions for the prompt transport of ^{18}F. In big Brazilian cities, the use of 2 wheel vehicles like motorcycles has proven to be an alternative to solve problems related to the transport of radioactive material of short half–lives.

As any other activity involving the transport of radioactive material, there is a need for a license to be granted by competent authorities. However, the use of 2 wheel vehicles for the transport of dangerous goods is not addressed in the transport regulations. Therefore there is a need of technical approach to obtain the necessary authorization. To accomplish this goal, it was simulated a shipment of radioactive material using a 2 wheel vehicle. In this simulation, 2 routes were chosen: the longest one, 45 km, and the shortest one, 12 km. The results were compared with the time spent when using a 4 wheel vehicle. With a 4 wheel vehicle, the time spent for the longest route was 75 min, in contrast to the time spent with a 2 wheel vehicle, 45 min.

All safety requirements (justification of practices, dose limitation and optimization of protection and safety) were taken into account [2,3].

Results: Based on existing official data on transport accidents, the risks for the transport of radioactive material using a 2 wheel vehicle was determined. Risk evaluation was based on a table of environmental aspects and impacts for different transport scenarios: routine, normal and accident conditions.

Discussion: Using Magnitude (M), Frequency (F) and Range (A) of occurrence as parameters, it was found out that the risk was considered significant in 3 situations, all of them in the order of 10^{-7}. According to CETESB, a state environmental agency, a risk in the order of 10^{-7} is acceptable for the transport of dangerous goods [4].

Calculating the dose which would be received by the driver of the 2 wheel vehicle, we found out that it would be necessary to put an additional shielding between the driver's back and the package.

Conclusion: The proposed paper will describe in detail the results for the simulation of transport of small quantities of radioactive material using a 2 wheel vehicle and the related risk evaluation. Compliance with national [2] and international requirements, especially the IAEA transport regulations for the safe transport of radioactive material, will be demonstrated.

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Implication of Amendment 49 in Brazilian radiopharmacy

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Amendment 49: Amendment 49, 8th february 2006, excludes from the monopoly of the Brazilian Goverment the production, the commercialization and the use of short half-life radiopharmaceuticals for medical, agricultural and industrial uses. The most recent modification of the Brazilian Constitution was gave for the alteration of the writing in the "alínea b", addition of a "alínea c" to the interpolated proposition XXIII of the *caput* of article 21 and for the new writing given to interpolated proposition V of the caput of article 177. Since its publishing a great effort of all regulatories agencies in Brazil have been made looking for the harmonization of national laws bu the Brazilian Nuclear Energy Comission, Health Surveillance Agency and Brazilian Pharmacopoiea.

The growth of PET-technology and consequently the use of FDG-18 and the radiopharmaceuticals in general, request a specific regulation. This regulation must be supported in the tripod: security, effectiveness and quality (FINN, 1999). In the United States, the radiopharmaceuticals are regulated under a number of agencies, because they are radioactive materials, and also are prescribed as medicine, being administered to human being. Finn (1999) alert, however, that an explicit need for the especific regulation. This necessity can be demonstrated by the signature in 21 november of 1997, in form of law, of the "Administration Modernization Act" (FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT, 1997) applied to the Food and Drug Administration (FDA). This act, in its structure, commands that the FDA, develops practical procedures and good manufacture practice for radiopharmaceuticals, including that used in PET. In Europe, the regulations (registration and production) is made by the publishing of various ECC rules (the first was in 1965's) that are published in the form of Directives and Decision. To date tere have been 33 Council Directives, one Council Decision and one Council Regulation. In order to clarify these, numerous guidelines have been published: 11 quality guidelines; 10 biotechnology guidelines, 7 pharmacotoxicology guidelines, 10 clinical guidelines (General), 12 clinical guidelines (Therapheutics) and 3 information on medical products.

Post-amendment Period: In Brazil, the first steps had started to be taken from this year. The first one of them, was the creation of the radiopharmacy subcommission, of the Brazilian Pharmacopoiea, responsible national agency for establishing the quality requirements that the medicines/drugs must obligatorily obey. These requirements include all the components used in the manufacture of medicines/drugs. Another action that deserves prominence, was the accomplishment of the "I Workshop on Radiofármacos", carried through Anvisa/CNEN (National Health Surveillance Agency/Brazilian Nuclear Energy Commission), in an attempt of free-cooperation in search of parameters. Beside this others initiatives are being taken and the PUCRS (Pontifical University Catholic of the Rio Grande Do Sul) in partnership with the CRCN-NE (Regional Center of Nuclear Sciences of Northeast) and Brazilian Pharmacopoeia is in advanced period of training to promote the I Course of Specialization in Radioparmacy. However, Brazil still very behind in technician-legislative terms, and does not have any regulation for radiopharmaceuticals production yet.

Prospective: An extremely important point in regards to radiopharmaceuticals is the education in radiopharmacy. As the production was always privative of the CNEN the formation was always incubency of the same one, however, with the opening of the monopoly in addition of the market, the demand will be increasing. Besides, there is no course in Brazil thats teach radiopharmacy themes,

even in the uiversities. As well an absolute lack of qualified professors, generates a preoccupying reality and that must be reviewed. However, nothing of concrete until the present moment really exists.

Conclusion: For years radiopharmaceuticals have been produced in Brazil, without any epecific regulation. The evolution of PET radiopharmaceuticals in general, has introduced a new class of drugs that requires especific regulation, production facilities and the most important, qualified professionals. Even in Brazil there are no technician-legislativeand any regulation a concerted effort by the various regulatory agencies has to be made to anchieve a safe and effective methodology (regulation) and in this way, permit Brazil radiopharamceutical production. Besides, is necessary introduce the theme radiopharmacy in the pharmacy schools programe, even in the post-graduated course and in this way, amplify the discussion. In fact, this actions will just minimize the problem stabilished in Brazil, but some thing has to be done and a more integrated work, including the Minisrty of Health should be proposed.

^{18}F-Lansoprazole: Chemical and biological studies towards the development of a new PET radiotracer

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Amyloid senile plaques are one of the major hallmark of Alzheimer´s disease. These structures are formed mainly by aggregated forms of the peptide Aβ1-42 [1]. Recently, benizimidazole and benzothiazole compounds have been assessed as potential PET tracers of senile plaques [2,3]. In this work we have assessed the binding affinity of lanzoprazole, chemical name: **1H-Benzimidazole, 2-((3-methyl-4-(2,2,2-trifluoroethoxy)-**2-pyridinyl), which is a drug clinically used to inhibit K+/H+ ATPase.

Chemistry. Labeling of the parent compound was performed by adding $Na^{18}F$ to an alkaline solution of lanzoprazole at two different temperatures (25 and 40ºC) the course of the reaction was controlled by TLC analysis. Separation of free remaining $^{18}F^-$ from the reaction mixture was made by using alumina columns.

Biology: Scatchard analysis was used to assess the binding affinity of 18F labeled lansoprazole for aggregated forms of Aβ. Also biological distribution and pharmacokinetic profile of the radiolabeled compound were evaluated in mice.

Results: Our experiments demonstrated that in vitro, 18F-lanzoprazole displayed high affinity for aggregated forms of the Aβ peptide, with inhibition constants Ki values in the nanomolar range. Biological distribution of the 18F labeled compound in mice at 30 min and 60 min showed kinetics profiles compatible with a PET tracers. Brain uptake was assessed by tow different methods yielding around 1% in the first 1 hour.

Conclusion: The encouraging in vitro and in vivo properties of lansoprazole support its further evaluation in transgenic models of Alzheimer disease, and subsequently in human subjects with amyloid deposition.

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Automatic synthesis of [11C]raclopride and initial clinical application on Parkinson's disease

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Background/Aim: Parkinson's disease is a common neurological degenerative disease. The change of dopamine D_2 receptors is of great importance in its mechanism. [^{11}C]Raclopride is a PET radiotracer for dopamine D_2 receptor. Establish a methods for automatic synthesis of [^{11}C]Raclopride on GE Tracerlab FX_C. Investigate the changes of dopamine D_2 receptor in Pakinson's disease patients after the introduction of piribedil with [^{11}C]Raclopride PET/CT.

Materials & Methods: [^{11}C]CO_2 produced by cyclotron was converted to [^{11}C]CH_3I via gas phase iodination. [^{11}C]CH_3I was bubbled into a reactor vessel contained 0.2ml of DMSO with 1mg precursor, demethyl-Raclopride, and 5μl of 8M NaOH. The reactor was heated to 70ºC for 5 minutes for labelling reaction and then the product was separated by HPLC. The HPLC eluent containing the product diluted by 80ml of water and passed through a plus C18 cartridge. The cartridge was washed with 10 ml water, 2 times then eluted by 1ml of ethanol. The ethanol was diluted with 10ml saline and the mixture passed through a 0.22μm filter to a sterilized vial. The final product was analysed by HPLC and had sterilization and pyrogen test.

6 patients of Parkinson's disease without therapy, 4 patients after piribedil therapy with mean age of 66.6±7.20 and mean disease duration 2.6±1.33years and 4 volunteers with mean age of 69.75±2.63 took part in the test. All of them underwent [^{11}C]raclopride PET/CT examination, with ten serial 1-minute, ten 2-minutes, and thereafter six 3.33-minutes time frames over the period of 50 minutes, providing a total of 26 time frames. After reconstruction, 16-26 frames were selected to calculate the bindings. The [^{11}C]raclopride binding index was defined as an uptake ratio of striatum to cerebellum.

Result: Total synthesis time from transfer [^{11}C]CO_2 to synthesis finished is 40min. The final yield without decay corrected is about 5%. The radiochemistry purity is more than 98%. The final product passed sterilization and pyrogen test.

In patients who received no therapy, the [^{11}C]raclopride binding index in the head of caudate nucleus, the anterior and posterior of putamen nucleus controlateral to the suffered limb is 2.94, 3.34 and 3.27 respectively, which is higher than that of the control group (2.54, 2.89 and 2.72). These two groups of character have statistical difference (p value being 0.046, 0.013 and 0.022), indicating that dopamine D_2 receptor was upregulated. In patients who received piribedil, the [^{11}C]raclopride binding index in the head of caudate nucleus, the anterior and posterior of putamen nucleus controlateral to the suffered limb is 2.59, 2.83 and 2.79 respectively, which is not higher than that of the control group (p value being 0.396, 0.276 and 0.2 respectively), indicating that piribedil can reverse the upregulation of dopamine D_2 receptor.

Discussions: Tracerlab FX_C is a commercial ^{11}C-methylation unit. It can proceed gas phase methyl iodide synthesis, methylation of precursor, HPLC separation and final product purification. All these processes are controlled and recorded by a computer. During the synthesis, no manual command or operation is needed. This can guarantee the quality of the final product. The synthesis method is established according to some early reported methods. [1] Many new methods to improve the yield and facilitate the synthesis are reported. [2-3] Further researches based on these reports on this system is being done.

Dopamine D_2 receptor is upregulated in the putamen nucleus in early Parkinson's disease patients. Piribedil can reverse the upregulation to D2 receptor. [4] ^{11}C-Raclopride can be used as quantitative analysis of dopamine D_2 receptor binding. [5]

Conclusion: A fully automatic method for synthesis of [^{11}C]raclopride was established. The final solution can be obtained in 40 min after the end of bombardment (EOB) with a final yield of 5% (without decay corrected). [^{11}C]raclopride PET/CT imaging can be used as a method to evaluate the threapy of Parkinson's disease.

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Radiolabelled oligosaccharide probes: An approach for infection imaging

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Aim/Background: Acute gastrointestinal infections due to rotaviruses and other enteric pathogens are major causes of morbidity and mortality in infants and young children throughout the world. The oligosaccharide fraction of human milk bear structural homology to cell surface glycoconjugates and used as receptors by pathogens which protect nursing infants from infections [1]. The similarities between cell surface glycoconjugates and oligosaccharides in human milk strengthen the idea that specific interactions of those oligosaccharides with pathogenic microorganisms do occur preventing the attachment of microbes to epithelial cells. Streptococcus pneumoniae and Haemophilus influenzae are major respiratory pathogens. They attach to the mucosal surfaces of the respiratory tract. This attachment is the first contact with the host tissues and may determine whether the bacteria will colonize the mucosa and cause infection. Conversely, if attachment is inhibited, the infection may be prevented. The free oligosaccharide blocks adhesion. So does human milk, which contains the receptor oligosaccharides. More than 130 lactose-derived oligosaccharides have been identified in human milk. There is the striking evidence that human milk oligosaccharides are potent inhibitors of bacterial adhesion to epithelial surfaces, an initial stage of infective processes. Therefore, these oligosaccharides are considered to be soluble receptor analogues of epithelial cell surfaces participating in the non-immunological defense system of human milk-fed infants.

About 130 oligosaccharide complexes have been isolated and characterized from human milk [2]. The presence of oligosaccharides binding proteins (eg.Cym E and Cym B) in bacterial membranes have also been reported [3]. The binding of Streptococcus pneumonia, enteropathogenic E.coli and Haemophilus to their receptors is inhibited by human breast milk oligosaccharides [4]. The binding of oligosaccharides to highly specific recognition receptor molecule lectin is known to be present over bacterial membrane.

Maltose binding protein bound to beta-cyclodextrin has two globular domains – how they are oriented in this complex was determined by solution NMR methods based on dipolar coupling measurements. The maltose and β-cyclodextrin binding through residues Asp 41 and Ser 211 are known as MBP backbone. The distance between the C atoms of Asp 41 and Ser 211 in the maltose-MBP and β -cyclodextrin-MBP complexes is 15 and 24 A, respectively. The distance between the hydroxyl group of Ser 211 and the carboxyl carbon of Asp 41 in the maltose-MBP and b-cyclodextrin complexes is 11 and 23 A, respectively [3,5]. The presence of free hydroxyl groups for cyclodextrin metabolism in periplasmic and cytoplasmic spaces, suggested the transport of these molecules through outer and inner membranes of gram –ve and gram +ve bacteria. With this background studies were undertaken to utilize β-cyclodextrin after radio labeling with $^{99m}TcO_4$ as oligosaccharide probe for infection imaging.

Methods and materials: The labeling of β-cyclodextrin derivative was done by stannous chloride reduction method, using freshly eluted $^{99m}TcO_4$ from Amarsham ^{99}Mo-^{99m}Tc generator. The quality control procedures were followed. The assessment of radiopharmaceutical purity was evaluated using ITLC. The Images were taken at different time intervals for evaluation.The Clinical ethical clearance & approval from Drug controller of India was obtained.

Results: The labeling efficiency $^{99m}TcO_4$ to β- cyclodextrin was more than 97%. Increased uptakes of labeled β-cyclodextrin in infected areas were visualized in different cases were observed.

Discussions: Patients with proven infections, by hostopathology, were compared, which confirmed our findings. Some of our cases were compared with ^{99m}Tc labeled leukocyte, ^{99m}Tc MDP and ^{99m}Tc(V) DMSA imaging. Our results confirmed the accumulation of ^{99m}Tc-β cyclodextrin in infected areas and the early images obtained can also be taken as positive sign. The labeling procedure is cheaper; less cumbersome and early images are comparable with other imaging modalities.

Conclusions: The localization of ^{99m}Tc-β cyclodextrin may be possibly due to either its binding to sialoprotein receptors or the maltose binding proteins present on gram + ve or/and gram –ve bacterial membrane as reported in the literature.

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Radiolabelling of DOTA-derivatized peptide D-phe¹-Tyr³-octreotide (TOC) with ^{68}gallium: Initial experience

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Introduction: Positron Emission Tomography (PET), a molecular imaging technology, has revolutionized the Nuclear Medicine Imaging with the availability of short half-life and positron-emitting tracers. Radionuclide generators provide cyclotron–independent accesss to PET radiopharmaceuticals. ^{68}Ge/^{68}Ga generator is such an example to access PET radiopharmaceuticals which provides an excellent source to wide spectrum of tumor specific peptides, antibodies, fragments for diagnosis. The parent ^{68}Germanium has a half-life of 270.8 days and daughter ^{68}Gallium of 68 minutes. This generator can be eluted every 3 to 4 hrs during the day as per requirement. ^{68}Ga-DOTATOC is a tracer which reflects the expression of somatostatin receptor 2 (SST2) of neuroendocrine tumors.

Materials and Methods: Laminar Flow Cabinet, ^{68}Ge/^{68}Ga generator, TLC Scanner, Dose Caliberator, Survey Meter etc. AR grade chemicals and Milli-Q water, AG 50W-X8, a heating block, sterile vials, C-18 cartridge, Phenomenex Strata-X Tubes, 30 mg, Millex GV filter- 0.22µm, syringes, lead pots etc.and DOTA- derivatized peptide D-phe¹-Tyr³-octreotide (TOC).

^{68}Ge/^{68}Ga is eluted with 0.1N HCl to obtain ^{68}Gallium. Eluate is concentrated on an cation ion exchanger. Two concentrations of DOTATOC (40 and 60µg) were used for radiolabelling with ^{68}Ga at 125-127°C. Reaction was allowed to take place for 10 and 15 minutes and then was purified on a C18 (reverse phase) column to remove the unlabelled peptide. The quality control of ^{68}Ga-DOTATOC was performed to know the radiochemical purity (RCP), pH, clarity etc.

Results: pH was between 6.5-7.0, RCP >99%, %yield – 60 -70%, ^{68}Germanium content was found to be negligible in final product.

Discussion: Radiolabelled ^{68}Ga-DOTATOC showed good binding with 60µg of peptide and at 10 minutes reaction time. This showed high radiochemical purity and could be used for routinely for the diagnosis of neuroendocrine tumos. At our centre 2-3 patients are done on alternate day. The handling is performed in a semi-automated system with minimal dead volume and metal- free materials in all the chemicals, except for those used for handling the final product.

Conclusion: ^{68}Gallium labelled DOTATOC can be prepared easily and used successfully for patients making use of ^{68}Ge/^{68}Ga generator. For example in one patient [^{18}F] FDG uptake was normal and ^{68}Ga-DOTATOC showed a focal area of increased radiotracer uptake in the uncinate process of pancreas consistent with the presence of an insulinoma.

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Preliminary studies on a rapid radiosynthesis procedure for [^{18}F] FHBG using a non-HPLC purification technique

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Various research groups have presented methods for the radiosynthesis of [^{18}F] 9-(4 – [^{18}F] Flouro-3-hydroxymethylbutyl) guanine ([^{18}F]-FHBG) [1,2,3]. However, all the procedures have long radiosynthesis time (60-100 minutes), poor yield (< 15% decay corrected) and elaborate purification procedures. Recently, Ponde et.al [4] have reported a microwave assisted radiosynthesis procedure with a radiochemical yield (decay corrected) of 12±5% (n = 35) and a total synthesis time of 55-60 minutes. Being a useful PET-radiopharmaceutical, [^{18}F]-FHBG, it is necessary to develop a simpler and more efficient radiosynthesis procedure. Here, we report, our preliminary attempts on a fully-automated radiosynthesis of [^{18}F]-FHBG with a much shorter synthesis time and a higher radiochemical yield. We have also attempted purification using an indigenously developed combination-column composed of anion exchanger and neutral alumina with a view to avoid the cumbersome HPLC method.

$^{18}F^-$ produced in the cyclotron [^{18}O (p, n) ^{18}F] is trapped in the small anion exchange column (Chromafix 45-PS-HCO_3) and eluted into the reaction vessel in the form of TBA^{18}F (Tetrabutyl Ammonium Fluoride). Excess DNA-grade acetonitrile was added and the mixture distilled azeotropically until the TBA^{18}F was dry. Nucleophilic fluorination of the precursor, N^2- (p-anisyldiphenylmethyl) 9-[(4-tosyl)-3-p-anisyldiphenylmethoxy-methyl] guanine (Tosyl-FHBG), 25mg/0.6 ml, (0.4 ml dry MeCN+0.2 ml EtOH) takes place at 125˚C for 15 minutes. The reaction mixture is brought to near-dryness with heat and vacuum while passing He-gas. 1ml HCl (1M) is then added and heated to 115˚C for 10 minutes to hydrolyze the methoxytrityl (-MTr) protecting group. The reaction mixture is cooled and passed through the purification column described above. The reaction vessel is rinsed with 1 ml 35:75 acetonitrile:water mixture and passed through the column. Finally [^{18}F]FHBG was eluted with 12 ml eluent (10ml 50% ethanolic water + 2ml acetonitrile) into the product vial already containing 1.5 ml 10% NaCl and 0.5 ml 1(M)NaH_2PO_4 to maintain the pH and isotonicity of the product.

The final product is then dispensed through 0.2µ filter into sterile and bacterial endotoxin free evacuated vials. QC analysis is carried out to confirm the radiochemical purity by TLC in 95:5 methanol: NH_3, radionuclidic identity by $T_{½}$ measurements, checking the pH by pH paper and clarity by visual check. Sterility and bacterial endotoxin tests were carried out on samples after the radioactivity has decayed.

The [^{18}F]-FHBG synthesized by our procedure is satisfactory giving a clear, colourless product. The pH is ~6.0 and the RCP of [^{18}F]- FHBG so far we have achieved is 70±5% (R_f of [^{18}F] FHBG in MeOH: NH3 [95:5] is 0.55-0.75) and it was verified by TLC of the reference standard (^{19}FHBG) using UV active TLC sheets (Fig. 1). $T_{½}$ measurements were found to be 110±5 minutes indicating that the product was labeled with ^{18}F. All the batches have passed the sterility and bacterial endotoxin tests. The total synthesis time is 45±5 minutes and the radiochemical yield is 20±5 % (n=5, without any decay correction).

Our studies show promising results for developing a fully automated synthesis procedure very similar to FDG synthesis procedure and can be easily carried out in a commercial FDG synthesis module.

Regarding radiochemical purity, one very polar radioactive impurity is observed at the point of spotting in TLC, which can be minimized by increasing the lipophilicity of the eluting media from the purification column. It is not TBA^{18}F as verified form further cross check. It is most possibly some reaction intermediate.

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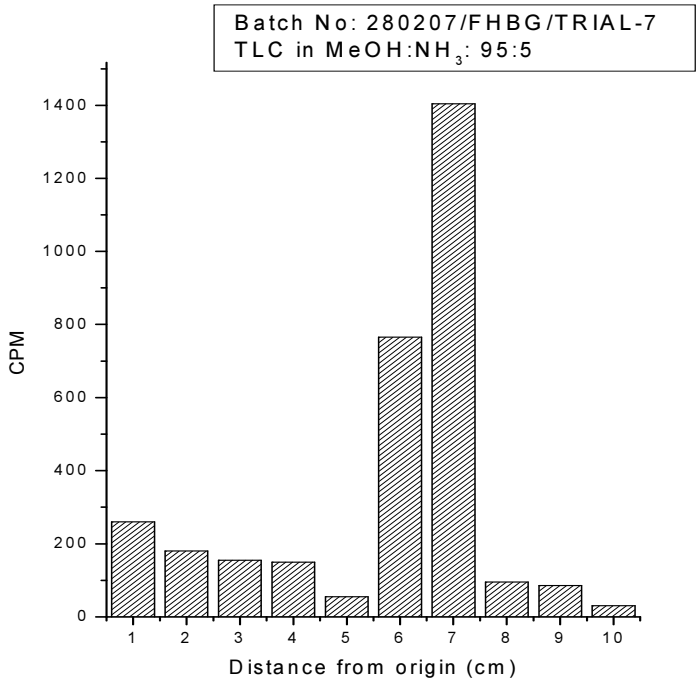

FIG. 1. TLC of [^{18}F] FHBG in MeOH: NH3 (95:5) (R_f of [^{18}F] FHBG 0.55-.0.75).

Multi-purpose synthesis module for preparing [F-18]–labeled compounds

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The PET-radiochemistry at the Medical Cyclotron Facility located in the basement of the Tata Memorial Hospital Annexe building has two dedicated ^{18}F-FDG synthesizers and a ^{11}C-methylation module (all from Nuclear-Interface, Munster, Germany). Two batches of ^{18}F-FDG, between 25 – 40 GBq each, are prepared daily for supply to various hospitals. With researchers, elsewhere, demonstrating the promise of ^{18}F-FLT and ^{18}F-MISO, we felt the need for a general purpose nucleophilic synthesis module for preparing these ^{18}F-PET-tracers. We explored the possibility and carried out the necessary changes to adapt the ^{11}C-methylation module for fluorination.

The ^{11}C-methylation module was adapted for nucleophilic fluorination by re-routing the tubings, valves and re-writing the time lists for the various steps, involving distillation, drying, S_N2 substitution, hydrolysis, rinsing, washing etc., taking into account the geometry of the reaction vessel, heating and cooling rates and other parameters. Parts of the module required for trapping and processing the ^{11}C-CO_2 were bypassed and provision was made for introducing an anion-exchange column for trapping the $^{18}F^-$. Similarly, changes were made providing options for the purification of the product through a combination column or collection of the reaction mixture for further analysis/purification by HPLC. Fig 1 and Fig 2 show the schematic diagram of the module before and after the changes.

New time-lists were written for the preparation of ^{18}F-NaF, ^{18}F-FDG, ^{18}F-FLT, ^{18}F-FMISO and ^{18}F-FHBG. The time lists were optimised for the different reaction conditions depending on the precursor used. After every synthesis, an automated cleaning run was carried out wherein the tubings, reaction vessel and reagent containers in the module are rinsed with acetone and dried with helium. The product vial was sterilised with ethanol.

Precursors, TBA-HCO_3 and $^{18}F^-$trapping columns required for the synthesis of the above PET-tracers were procured from ABX-Chemcals, Germany. All other chemicals of and purification columns were were of pharma-grade and procured elsewhere

The modifications were essentially straightforward using readily available spare parts. The adaptation was successful and the module used for preparing the above ^{18}F-PET-tracers whenever required.

We have used the module to make over 80 batches of ^{18}F-NaF, 30 batches of ^{18}F-FDG, 18 batches of ^{18}F-FLT, 15 batches of ^{18}F-FMISO and 8 batches of ^{18}F-FHBG. The yields were satisfactory The cleaning run is very satisfactory as no noticeable contamination is seen after it. ^{18}F-NaF was the simplest since no chemical processing was required.

With a demand for other [F-18]–PET-RPs, there is a need for modules which can handle the required chemistry and purification steps which cannot be carried out in dedicated FDG-synthesis modules. Further, due to space, weight and cost restrictions, it would not be economical to have dedicated modules for every [F-18]-PET-RP. With this in mind, manufacturers are now marketing general purpose fluorination modules that can be used for a number of [F-18] PET-RPs produced by nucleophilic substitution route.

The major concern raised by the radio pharmacists is whether there will be contamination of one [F-18]-RP with another produced in the same module, compromising radiochemical and

radiopharmaceutical purity. We have not found cross-contamination an issue, since the automated cleaning step is very satisfactory.

Our experience shows that it is possible, with some ingenuity, to fabricate multi-purpose synthesis modules, which can be used for synthesis of more than one [F-18]-labeled PET-RPs.

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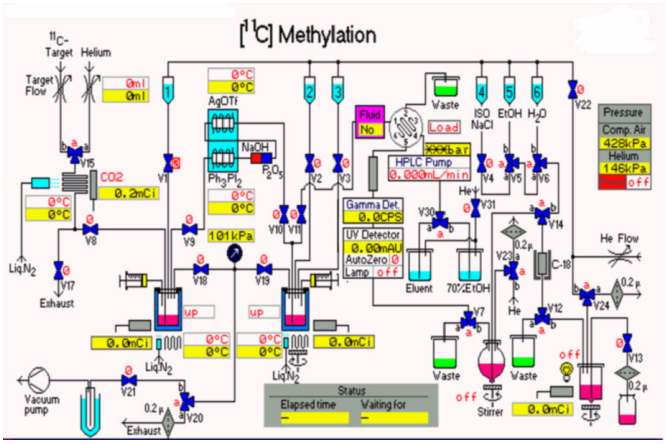

FIG. 1. Schematic of ^{11}C-Methylation module.

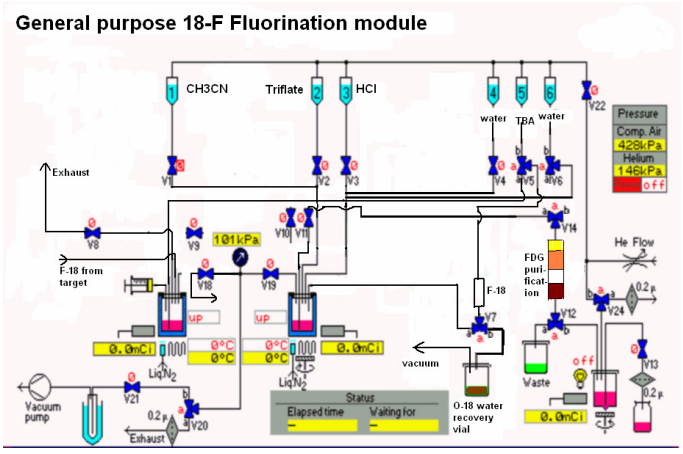

FIG. 2. Schematic of module adapted for general purpose fluorination.

Synthesis and in vitro/in vivo evaluation of [^{99m}Tc-EDDA-HYNIC]-NATE as a new radiopharmaceutical for somatostatin receptor scintigraphy

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Aim/Background: Radiolabeled somatostatin analogues have been successfully used for targeted radiotherapy and imaging of somatostatin receptor (sstr) positive tumours. In an effort to make available radiolabeled analogues with a broader spectrum and able to target other sstr in addition to $sstr_2$, [$DOTA^0$, 1-Nal^3]-octreotate has been recently developed [1]. In this study the preclinical evaluation of 1-Nal^3-Octreotate (NATE) labeled with ^{99m}Tc using HYNIC chelator and ethylenediamine-*N, N′* -diacetic acid (EDDA) as a coligands is described [2].

Methods and materials: Peptide was synthesized on a solid phase following typical Fmoc/Boc protection strategies (Fig. 1). Labeling with ^{99m}Tc was performed at 100°C for 10 min using $SnCl_2$ as reducing agent. Radiochemical analysis involved ITLC and HPLC methods. The internalization rate was studied in $sstr_2$ expressing AR4-2J and $sstr_3$ expressing human embryonic kidney (HEK) 293 cells. Biodistribution was studied in rats bearing AR4-2J tumour.

Results: [^{99m}Tc-EDDA-HYNIC]-NATE was prepared in high radiochemical yield and purity (>95%). The radiopeptide showed a fast and specific internalization into AR4-2J cells (15.17% ± 0.81% at 4 h). The internalization into HEK-$sstr_3$ cells was moderate and specific (4.56% ± 0.69% at 4 h). In animal biodistribution studies a receptor-specific uptake of radioactivity was observed in sstr-positive organs and also in AR4-2J tumour (1.83 ± 0.33 %ID/g).

Discussions: These data show that radioligand have a potential to target tumours with $sstr_2$ and $sstr_3$ expression, either alone or concomitantly with other subtypes.

Conclusions: [^{99m}Tc-EDDA-HYNIC]-NATE might prove to be useful in the diagnostic imaging of tumours expressing $sstr_2$ or additional receptor subtypes.

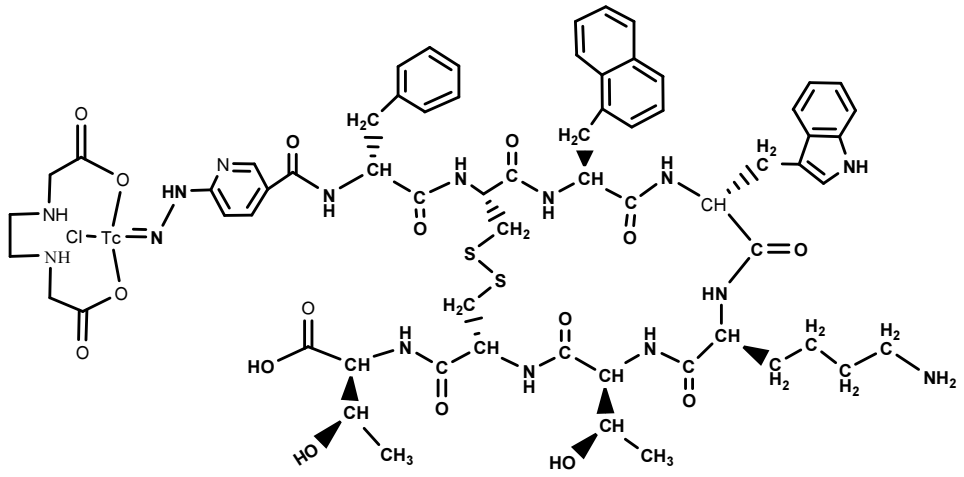

FIG. 1. Structure of [^{99m}Tc-EDDA-HYNIC]-NATE complex.

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Cyclotron production of no-carrier-added ^{64}Cu for cancer radiotherapy agent and positron emission tomography (PET)

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The Copper-64 physical-decay parameters ($T_{1/2}$=12,7 h, $E_{\beta+}$=0.66 MeV, $E_{\beta-}$=0.58 MeV, $I_{\beta+}$=19%, $I_{\beta-}$=40%, I_{EC}=41%) shows some potential endoradiotherapy applications in addition its usefulness as PET radiotracer [1] and could became an effective radiotherapy agent for cancer treatment. Copper-64 is widely labeled as DTPA-peptide, DOTA-peptide or monoclonal antibody on colon cancer studies. Copper-64 labeled antibodies have shown promising results as radioimmunotherapy (RIT) agent's [2].

Copper-64 was produced utilizing ^{64}Ni(p,n)^{64}Cu nuclear reaction. Natural nickel was electroplated successfully, 48 μm thick, onto a gold-coated copper backing slab. Bombardment of nickel plated target was performed with 16 MeV protons beams and a current of 200 μA. Natural nickel (99.99% purity) was purchased from Aldrich Chemical Company. Naturally abundant nickel (^{58}Ni 68.3%, ^{60}Ni 26.1%, ^{61}Ni 1.13%, ^{62}Ni 3.59%, ^{64}Ni 0.91%) was electroplated on a gold-coated copper backing (about 50 μm thickness, 11.69 cm^2). Appropriate quantities of nickel metal were dissolved in hot 6.0 M nitric acid and evaporated to dryness. The residue was treated with concentrated sulfuric acid followed by dilution with deionized water. The volume of the solution was adjusted to approximately 400 mL with deionized water. The pH was then adjusted to 3-4 with concentrated sodium hydroxide and the final volume was 450 mL, this solution was transferred to the cell and used for electroplating with a 50 mA·cm^{-2} DC current density at 45 ºC temperature. The complete electroplating process took 12 hours.

To take full benefit from related excitation functions and to minimize undesired radioactive impurities formation, entrance proton energy should be less than 16 MeV [3]. Physical nickel deposit thickness is chosen, for a given beam/target angle geometry, to provide a light-particle exit energy of about 3 MeV. According to SRIM code [4], target thickness has to be 480 μm for 90 ° geometry. It is advisable to minimize nickel deposit thickness (and hence reducing cost per enriched target) to perform irradiations on a 6° target geometry. In such case a 48 μm metallic deposit is recommended. For production of ^{64}Cu natural Nickel target was bombarded with 16 MeV protons for 1 hour with a current of 200 μA.

Irradiated nickel-electrodeposited targets on gold-coated copper backing were efficiently dissolved with a liquid flow-through stripper acidic cycle system (40 ml 6 N HNO_3 at 150ºC). Solution was evaporated to near dryness and resulting residues dissolved (25 ml of 10M HCl). Re-dissolved residues solution was heated to dryness and the new residue was then dissolved in 0.2 M HC1 in 96% methanol (prepared by mixing 2.5 m1 of 8.0 M HCl with 96 ml of methanol and 1.5 m1 deionized water. Volume changes arising from solvents mixing were disregarded).

For radioactive purification, elution through a 10 cm x 1 cm column anion exchange resin (1.5 ml/min flow rate) (Bio-Rad Dowex1x8, Cl^- form,100-200 mesh, packed resin treated with 1 M HC1 and then equilibrating with 0.2 M HC1 in 96% methanol). Each eluent was prepared as a percentage of the total mixed volume.

Separation of $^{64/57}$Ni and $^{55/57/58}$Co was achieved by successive washes of 0.2 M HC1 in 96% methanol (70 ml) and 1.3 M HC1 in 55% isopropyl alcohol (70 ml) respectively. The $^{64/61/60}$Cu was eluted using

0.5 M HCI in 50% isopropyl alcohol (20 ml).

Produced radioisotopes (^{60}Cu, ^{61}Cu, ^{64}Cu, ^{57}Ni, ^{56}Co, ^{57}Co and ^{58}Co) were detected by high purity Ge detector. The proposed improved separation technique allowed us to isolate cobalt and nickel from copper isotopes by eluting off from the column copper and cobalt separately.

The acid/alcohol procedure developed was used to separate ^{64}Cu from the irradiated enriched ^{64}Ni target. It can be observed that the ^{64}Cu fraction is radio nuclidecally very pure, no activities of Ni and Co were found on this fraction. In the Ni–Co fraction, $^{55/57}$Co, ^{57}Ni activities were found, while no ^{64}Cu was observed. By this procedure, the recovery of ^{64}Cu was better than 96%. The recommended procedure produces no-carrier-added ^{64}Cu from the enriched ^{64}Ni irradiated target, Co decontamination factor from Cu as well as the recoveries of ^{64}Cu and ^{64}Ni were higher than 96%.

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Estimating tumor/non-tumor uptake from radiolabeled monoclonal antibodies, based on scintigraphic imaging to avoid killing the animal models

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Introduction: Tumor imaging using monoclonal antibodies carring radioisotopes is a promising approach toward improving early diagnosis of cancer in nuclear medicine. A biodistribution study in animal models bearing tumors is one of the most important procedures in evaluation of fractional uptake of radiopharmaceuticals in the tumor and non-tumor organs. This examination is often performed on rodents to extrapolate potential doses of these agents to humans. It is obvious that if we can design a non-invasive method to evaluate biodistribution, the need for large amount of monoclonal antibody (which is expensive and very difficult to produce) and the number of animals to be sacrificed (due to moral considerations) is decreased. The aim of this study was to develop a new method to determine activities that accumulated in the main organs as well as tumor without killing the animals based on scintigraphy images taken by a double head gamma camera.

Material and Methods: The MAb PR81 that recently was produced against human breast tumor, radiolabeled with ^{99m}Tc. The complex was injected (20 µg PR81, 400µCi activity for each mouse) to 20 BALB/c mice with xenograft breast tumor (weight 25-35 g). The anterior and posterior images of mice were taken 16 hours after ^{99m}Tc-PR81 injection using a double head gamma camera. The images were transformed to PC after converting them to interfile format. Then the anterior and posterior images of each mouse were conjugated using the designed software. After that with drawing ROI around each organ as well as tumor, the counts were obtained considering calibration and background contribution. Then the mean and SD of counts was calculated for each organ. Meanwhile, the mice were killed, the organs dissected and were counted individually using a well counter and the mean and SD of counts was calculated for each organ. Finally, the measurements obtained by the both ways for tumor and main organs were compared. The Figure 1 shows a view of designed soft ware.

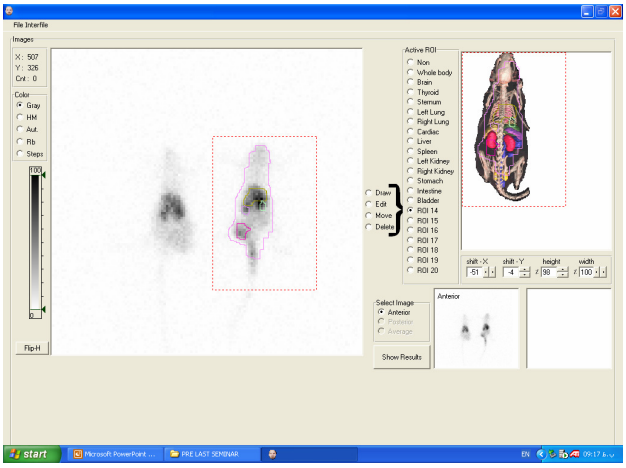

FIG. 1. A view of software designed to estimate tumor and main organs uptake.

Results: The comparison of the results obtained by both procedures showed that there is a significant difference between the measurements. It means that the new method cannot be replaced with the invasive one to estimate the absolute activity of each organ. This is mainly due to overlapping of the organs that causes error in calculations of accurate activity of each organ. However the new method can be used to compare the activity of tumor and main organs in relation to each other in order to evaluate the quality of new radiophamaceutical for targeting tumor as a basic parameter. The Table 1 shows the results of count measurements obtained by the non-invasive and the invasive methods.

TABLE 1. THE COUNT MEASURING RESULT 16 HOURS AFTER ^{99m}Tc-PR81 INJECTION IN TUMOR AND MAIN ORGANS OBTAINED BY THE INVASIVE AND SOFTWARE METHOD

Organ	Invasive Method		Software Method	
	Mean(CPM)	SD	Mean(CPM)	SD
Liver	1322	105	1851	166
Kidney	1183	94	1657	149
Lungs	205	16	287	25
Heart	75	6	105	9
Spleen	362	28	506	45
Intestines	1729	138	2421	217
Thyroid	463	37	518	58
Tumor	958	76	1341	120

Conclusion: The new method can be used to compare fractional activities of tumor and main organs to evaluate the quality of any new smart radiophamaceutical for targeting the tumor without killing the animals.

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Progress report of development of KIRAMS-30 cyclotron for RI productions in Korea

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Korea Institute of Radiological & Medical Sciences (KIRAMS) has been developing a 30 MeV cyclotron for RI production. Now the cyclotron is being installed at Advanced Radiation Technology Institute, Jeongeup. H- ions are injected from volume multicusp ionsource to cyclotron through the double gap buncher, solenoid, Q-doublet and spiral inflector. The isochronous magnetic field is generated with four sectored AVF magnet. The RF system is consists of two dees, four vertical stems and a capacitive coupler. 15-30 MeV ions are dually extracted using two horizontal movable stripper carbon foils. The cyclotron has four beam lines those are consist of steering magnet, Q-triplet, AC wobbler magnet and faraday cup.

After the installation, the cyclotron with various targets will produce F-18, C-11 for positron emission isotopes and I-123, Ga-67, Tl-201 for cancer therapy.

The role of iodine-131 MIBG and technetium-99m DMSA(V) in evaluation of malignant disease

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The aim of our work is to establish the protocols of preparation and application of 99mTc DMSA (V) and 131 I MIBG in the patient with malignant diseases.

Methods and Results: The radiopharmaceutical DMSA (V) was in house prepared as a sterile, pyrogen-free, freeze-drier product under nitrogen.

Each vial contain DMSA-1.0 mg and Stannous chloride dehydrate 0.4 mg with the final PH 2.0

Before labeling the kit was reconstituted by the addition of 0.5 ml sterile, pyrogen-free 3.5% NaHCO3. Reconstitution and labeling was performed by addition of sterile, pyrogen-free, isotonic sodium 99mtechnetium pertechnetate – 6 ml final volume. The product contains no antimicrobial preservative.

After incubation of 15 min. and before use, limpidity of the solution after preparation, pH (~8) and radioactivity was checked.

The quality control of this radiopharmaceutical was effected by:

1. Paper Chromatograpy (PC) using two solvens - acetone and 0.9% NaCl

2. Instant Thin Layer Chromatography (ITLC) using mixture of the n-butanol:acetic acid:water (3:2:3)

We evaluated the percentage of labeled complex technetium 99mTc DMSA (V), hydrolyzed and free technetium 99mTc. In every samples the labeling efficiency resulted more than 95%.

The normal *in vivo* biodistribution of this radiopharmaceutical was monitored in normal rats using imaging as well as counting dissected tissues, 2 and 4 hours after application.

The 131 I MIBG was prepared by iodination of meta-iodo-benzylguanidinum-sulfarte. 3mg MIBG and 6mg ammonium sulfate were dissolved in ethanol-water 1:1 mixture and 1% CuSo4. Adding 2.5 – 10 mCi Iodine and evaporing the solution carefully, under infrared lamp for 45-60 minutes was performed radiolabeling procedure. After evaporation, the vial was placed into the furnace for a labeling reaction by heating for 40 minutes at temperature between 166-175^{o}C. After labeling the vial was cooled completely, measured the activity of the melt and dissolved with 3-4 ml of Walpole buffer pH-5.0 by vortexing.

The quality control of 131 I MIBG was effected by:

1. Paper Chromatography (Whatman- FN4-TLC) using abs.Ethanol:ethylacetate mixture 1:1

2. Polygram-Sil-NHR using mixture of the n-butanol:acetic acid:water (5:2:1)

We evaluated the percentage of labeled complex and in every sample the labeling efficiency resulted more than 95%.

The normal *in vivo* biodistribution of this radiopharmaceutical was monitored after application in normal rats using both imaging and counting of the dissected tissues.

99mTc-DMSA(V) and 131 I-MIBG was injected in the patient following the indications:

- conformation in suspected neuroectodermally derived tumors including neuroblastoma, phaeochromocytoma and medullar thyroid carcinoma;
- staging of the disease
- before and after surgery of the primary tumour
- follow-up after treatment to exclude a sub-clinical relapse, especially in the bone marrow and also in the case of any clinical abnormality during follow-up, particulary bone pain.

We present the patients with MTC, where in different time points after surgical removal of the tumor, using our radiopharmaceuticals, described above. We were able to detect local recurrence of the tumor, as well as cervical and mediastinal lymph node, lung and bone metastases.

Results obtained by scintigraphy are in good agreement with the data obtained by CAT, radiological examination, bone scintigraphy and the serum levels of CEA. They can be use for diagnosis of primary medullary thyroid carcinoma (MTC), as well for the detection of residual tumor tissue after surgical resection, and detection of metastatic deposits.

When data about the basal and follow-up levels of thyrocalcitonin are unavailable, we are monitoring successfully the patients using ^{99m}Tc DMSA (V) scintigraphy.

Second-generation ^{99m}Tc-radiopharmaceuticals for molecular imaging era

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This is a mini-review of the second generation ^{99m}Tc-radiopharmaceuticals for molecular imaging era. Underlying concepts, methods and potentials of a range of ^{99m}Tc-based molecular imaing probes will be discussed.

From the First Generation to Second Generation ^{99m}Tc-Radiopharmaceuticals

It is generally agreed that future of nuclear medicine should be focussed on molecular imaging and therapy. This concept is also reflected in the development of ^{99m}Tc-radiopharmaceuticals. There is a shift from the first-generation ^{99m}Tc-radiopharmaceuticals, biodistribution determined exclusively by their chemical and physical properties, to second-generation ^{99m}Tc-radiopharmaceuticals. But for the second-generation radiopharmaceuticals their ultimate distribution is determined by their receptor binding or other biological interactions [1]. Target specificity is achieved by linking targeting molecule, which might be peptides, antibodies, hormones or proteins, to a ^{99m}Tc-complex.

New ^{99m}Tc-cores

Few new Tc-cores have been developed such as [^{99m}Tc(CO)$_3$]-core, ^{99m}Tc-HYNIC core, which have significantly enriched ^{99m}Tc-radiopharmaceutical chemistry. Though ^{99m}Tc-oxo core is still remain as the main ^{99m}Tc-core for commercially available kits, there is a great need for the development of kits based on new ^{99m}Tc-cores to maintain the status of ^{99m}Tc-radiopharmaceuticals as the work horse of nuclear medicine in the molecular imaging era.

Labelling Approaches

Generally, two approaches have been used to design second-generation ^{99m}Tc-tagged radiopharmaceuticals: the integrated approach and the bifunctional chelators approach [1,2]. The integrated approach involves the replacement of part of a known high-affinity receptor ligand with the ^{99m}Tc chelate. The bifunctional approach uses a high binding affinity receptor ligand as the targeting molecule, a bifunctional chelator (BFC) for the conjugation of the receptor ligand and the chelation of the radionuclide (^{99m}Tc), and a linker as the pharmacokinetic modifier. In this approach, the technetium chelate is often far apart from the receptor binding motif to minimize possible interference of the receptor binding by the technetium chelate [1,2].

New ^{99m}Tc-labelled Biomarkers

There is an enormous development in discovery of biomarkers (clinical, prognostic, preclinical and predisposition markers) in post-genomic era [3]. Tremendous advances in molecular biology have revealed the sequence, structure, and function of genes and proteins, the physicochemical properties of cellular ligands and receptors, and crucial details about the cell cycle and genetic mutations. In some way, radiopharmaceutical research can take advantage of the new development in the therapeutic pharmaceutical industry, using these lead compounds as a platform and modifying them with a BFC for radiolabeling. The ability to noninvasively monitor cell biology in vivo is the goal of molecular imaging.

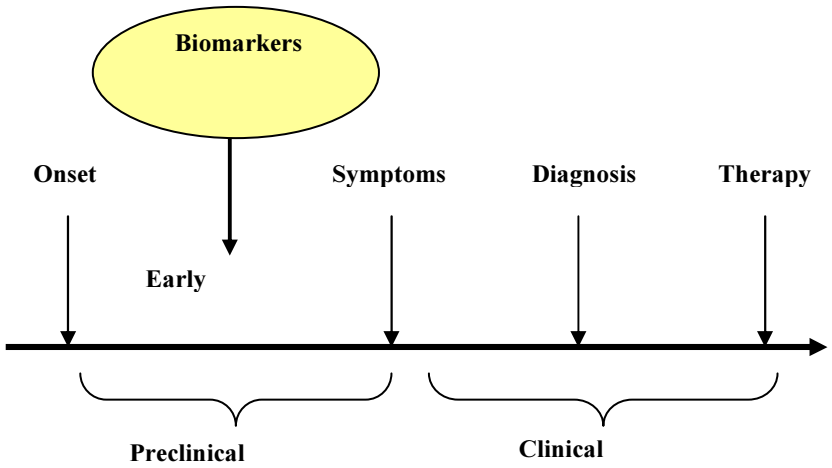

FIG. 1. An epidemiological perspective of cancer progression.

By utilizing these new concepts and technologies, nuclear medicine has the potential to image functional and metabolic processes as well as structural morphology by using second-generation ^{99m}Tc-radiopharmaceuticals and also for the early detection of certain diseases before the sympotms developed [4].

TABLE 1. SELECTED EXAMPLES OF ^{99m}Tc RADIOPHARMACEUTICALS WITH NEW ^{99m}Tc-CORES AND SECOND- GENERATION ^{99m}Tc RADIOPHARMACEUTICALS

^{99m}Tc-Core	**Targeting Molecule**	**Target**	**Reference**
^{99m}Tc-HYNIC	Annexin V (2nd generation)	Apoptosis	[5]
	Octreotide (2nd generation)	Neuroendocrine tumors	[6]
$\{^{99m}Tc^{I}(CO)^{3}\}^{+}$	Lantheonine (Tc-essential)	Kidney	[7,8]
	Neurotensin (2nd generation)	Pancreatic adnocarcinoma	[9]
$[^{99m}Tc^{III}\equiv N]$	NOET (Tc-essential)	Myocardial perfusion	[10]
$[^{99m}Tc^{V}=O]^{3+}$	Aminoethyl estradiol	Endometriosis	[11]

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Disruption to daily PET radiopharmaceutical production arising from cyclotron & synthesis module problems, corrective actions taken and associated downtime

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In the past 5 years there has been a significant increase in the acquisition and use of "small" cyclotrons devoted exclusively to use by physicists and chemists in hospitals and institutions for the production of biomedically useful PET radionuclides. These cyclotrons are reliable, simple to operate and automated to a great extent.

The continual operation of the PET radioparmaceutical production depends heavily on the sustained operation of the cyclotron and its associated supporting infrastructure such as the cooling, power, exhaust, gas supply, airconditioning and radiation monitoring systems. These systems need to function within their specification to ensure a smooth PET radioparmaceutical production.

We present our experience in opearting, performing the various preventive maintenance and dealing with the cyclotron, its associated systems and PET synthesis module failures, highlighting the specific part failures, faults, corrective action taken and the corresponding downtime that were encountered. The operation team comprising of physicist, radiochemist, technician and medical technologist was new and learning their task in operating the PET radiopharmaceutical facility. Our experience in training the team on the job is also presented.

The running in period for the cyclotron and the associated equipment was about 2 months. There were some initial teething problems we faced during the first 6 months of operation. This resulted in several PET radiopharmaceutical production delays. These problems were solved during the first cyclotron preventive maintenance which was conducted after 6 months of operation. The shutdown was for 5 working days during which over a hundred maintenance steps were undertaken by the local vendor's engineers and the physics team of the department.

We have had a total of 6 cyclotron down times where there was no production on these days and several cyclotron delays of up to 4 hours over the next 3 years of operation.

The daily operation of the cyclotron and the synthesis unit includes a series of checks stipulated on a checklist we developed. The steps involved in preparing and operating the cyclotron and PET synthesis module are also presented.

The costs and benefits of the Quality Management and best practice of [^{18}F]FDG manufacturing

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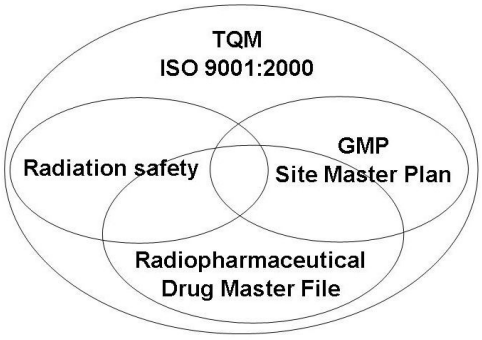
Background: The PET radiopharmaceuticals production facilities of present company BIONT have been planned and built during the years 1999-2004 under the support of IAEA.[1] Specificity of their construction in our case was a lack of nuclear research infrastructure and experience in this field, reconstruction of the building dedicated for completely unlike purposes, unexpected opposing of public, serious enhancement of principal regulation acts during the planning and establishment period, and last not least the rigorous requests not only from the side of supervising authorities but also of the investor (Slovak Office of Standards, Metrology and Testing). This all together predetermined the facility design and production launching:

- a full potential scale of the PET radionuclides production, either for in-house application or outer distribution,
- benchmarking, implementation of the best practice from European producers,
- high level of automation control both at production and quality control,
- the radiation protection limits dictated by citizen individuals safety and consideration of low background for nearby metrological laboratories.

Methods: From the design qualification stage it was decided to follow the ISO 9001:2000 quality management system as an umbrella for all good practice activities, the GMP and GAMP in particular, and as a safeguard for the patients investigated by PET/CT tomography and the environmental issues. The overlay of ISO 9001:2000 quality management system and cGMP is well recognized [1-3], and important specifity is added by radiation safety rules. Production of PET radiopharmaceutical is specific not only in respect of radioactive and trace concentrations of API, what is typical for immense majority of radiopharmaceuticals, but due to very limited possibilities of corrective measures in case of non-compliance, and individual responsibility of the production and QC operators. It means, the preliminary stages of order acceptance, radiopharmaceutical preparation and compounding, and also the quality assurance were implemented in the quality assurance scheme [4].



Results and Discussion: In present paper, the process of step-by-step satisfaction of the principles are illustrated on the [^{18}F]FDG production.

- Advanced quality control of imported FDG:

[1] IAEA Technical co-operation task SLR/2/002 „Radiochemical facilities for production of medical radionuclides“

LC-MS and HPTLC analysis of radiochemical purity proved a high radiation and chemical stability of [^{18}F]FDG even close to expiration time.

- Personnel training and qualified persons assurance:
  Among the qualified staff of physicists, radiochemists and pharmaceutists, three qualified persons are requested by the Slovak drug production legislation, and they were prepared in advance in specialised courses and in external institutions producing and using radiopharmaceuticals. Preparation of directive documentation (directives and standard operation procedures) were important part of personell training.

- Design qualification:
  The ventilation system, commercial shielded cells for the clean rooms of class „C", and especially the devices dedicated to automated dispensing in class "A" aseptic environment, passed scrupulous design qualification, and also operational qualification procedures.

- Quality assessment and preventive measures techniques:
  Statistical methods (Shewhart regulation diagrams, ANOVA and Bayesian sampling plans) were implied to substantiate rational quality assessment.

- Radiation safety and parametric production process monitoring:
  A multifaceted company information system consists of subsystems of the production information system, the radiation monitoring system, LIMS, and the system of material and financial accounting. They ensure registration according to GMP and ISO 9001 rules, and documentation starting with the order acceptance till the issues of delivery documents.

- Design and development of radiopharmaceuticals:
  The practice of development of a new radionuclide and tradiopharmaceuticals production is set on validated results of product development.

Notable benefits of total quality management are documented by practical achievements in the personnel training, stress minimization, and last not least the paper work elimination The confidence of customers seems to be the most long-range run.

Conclusion: The total quality management was proved as a reasonable extension of the good manufacturing of radiopharmaceuticals towards reliability of the just-in-time production, environmental concerns and customer satisfaction – the parameters important for good economical issues and market competitiveness.

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Is Tc-99m glucarate a tracer of tumor necrosis? Comparison with F-18 FDG PET in a breast cancer model and preliminary clinical experience

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Aim/Background: Solid tumors often exhibit regions of rapidly proliferating cells and regions of slow cell growth or dying cells. Besides, the MDA-MB-435 tumors were characterized by rapidly growing cells on the perimeter, with a centralized region of necrosis. In this study, two radiopharmaceuticals were examined for tumor uptake and distribution in MDA-MB-435 human breast cancer SCID mouse xenografts. It is well known that ^{18}F-FDG is rapidly internalized through the GLUT-1 transporter where it enters the glycolytic pathway in metabolically active cells without continuing the next step in glycolysis.

Glucaric acid or Glucarate is a natural catabolite of glucuronic acid metabolism. The potential structural similarity of ^{99m}Tc-Glucarate to that of fructose suggests that it may enter cells by a sugar transport system. Once inside the cell, ^{99m}Tc-Glucarate is postulated to interact with histones through charge interactions. ^{99m}Tc-Glucarate has been used to detect myocardial and cerebral necrosis and has also been demonstrated to accumulate in tumors [1,2]. The objectives of this paper was to study the effects of breast cancer microenvironment on the localization and uptake of radiolabeled imaging agents ^{18}F-FDG and ^{99m}Tc-Glucarate in a preclinical mouse model and to evaluate the potential of ^{99m}Tc-Glucarate for imaging breast cancer patients.

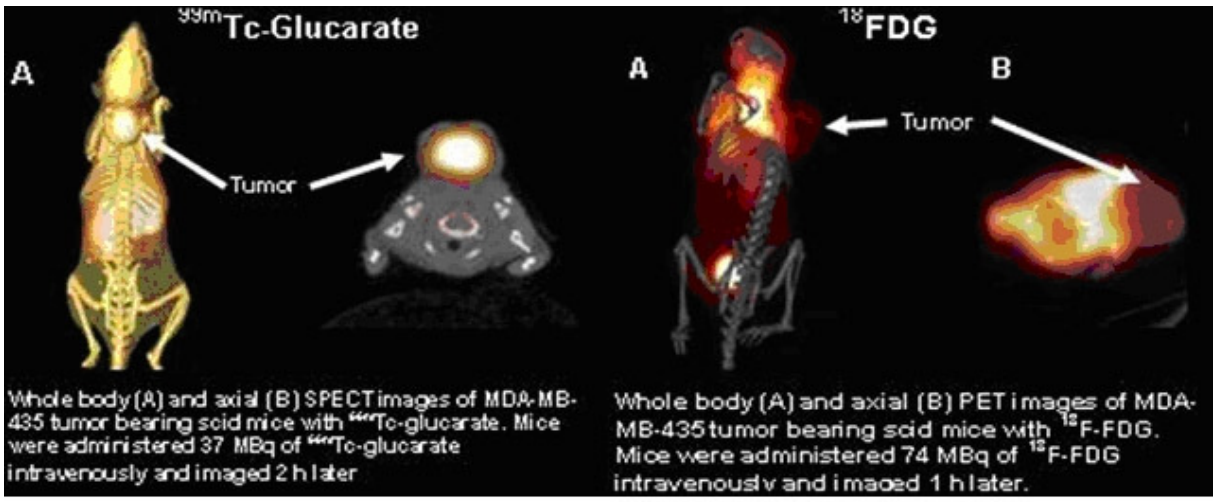
Methods and materials: ^{99m}Tc-Glucarate was prepared from cGMP glucarate formulation kits. Biodistribution and micro PET-CT, micro SPECT-CT and micro magnetic resonance imaging studies were performed in CD-1 normal mice and MDA-435 breast cancer xenografted SCID mice, respectively. Tumor bearing mice were injected with 74 MBq of ^{18}F-FDG and 37 MBq of ^{99m}Tc-Glucarate. Micro PET-CT scans were performed on anesthetized mice 1h post infusion of ^{18}F-FDG, while micro SPECT-CT imaging was performed 2h post infusion of ^{99m}Tc-Glucarate. Whole-body images of three female patients with locally advanced breast cancer were acquired 6 hours after the injection of 1110 MBq of ^{99m}Tc-Glucarate. Additionally, planar images of the thorax and breast were performed.

Results: The radiochemical purity of ^{99m}Tc-Glucarate formulation was greater that 95% and exhibited an in vitro stability of 24 h. Biodistribution studies in normal mice demonstrated rapid whole body clearance with 92.38±1.17 %ID of the radioactivity excreted 3 h post injection (p.i.). Radioactivity in the normal organs was low except for the kidneys, which exhibited 21.06±3.86 and 5.12±0.69 %ID at 1 and 3 h PI, respectively. A small portion of the radioactivity was excreted through the colon, which had 3.48±0.95 %ID at 1 h and 0.48±0.05 %ID at 3 hr p.i. Micro SPECT-CT images obtained with ^{99m}Tc-Glucarate displayed a more uniform uptake of activity across the volume of the tumor. Non-tumor ^{99m}Tc-Glucarate tumor accumulation was observed in the GI tract and in the kidneys.Micro PET-CT images revealed high uptake of ^{18}F-FDG around the periphery of the tumor with less uptake in the center of the tumor. Micro MR images of the tumor provided anatomical evidence for a region

of necrosis in the center of the tumor. ^{99m}Tc-Glucarate scans in patients with advanced breast cancer showed at 6 hours an accumulation of radioactivity at primary and secondary lesions of all patients in the following locations: primary tumor (n=2) and supraclavicular region (n=2). Also there was kidney and gastrointestinal uptake. One patient was staged as IIIb and the others were stage IV. Non of them received radiotherapy or chemotherapy prior to imaging. All lesions were confirmed by biopsy.

Discussion: Whereas FDG PET images showed accumulation in viable tumor cells, micro-SPECT images revealed that the distribution of ^{99m}Tc-Glucarate within the tumors was not greatly influenced by cellular necrosis or potential hypoxic center of the tumor. Metabolically active cells pump in the glucose analog ^{18}F-FDG, which becomes trapped in the cytoplasm. However, there is low demand for this tracer in necrotic cells leading to background levels of radioactivity in the necrotic centers of the MDA-MB-435 tumors. The lack of ^{18}F-FDG uptake in the tumor centers correlates with the necrotic tissue detected by micro MRI. In normal tumor cells ^{99m}Tc-Glucarate is postulated to be transported into the cell by the fructose transporter. In necrotic cells, ^{99m}Tc-Glucarate rapidly diffuses into the cell through its compromised membrane and is thought to associate with positively charged proteins such as the histones. Higher levels of radioactivity associated with necrotic tissue within the tumor correlated with MR images.

Conclusion: ^{99m}Tc-Glucarate has the potential to constitute a clinically relevant imaging agent for patients with breast cancer. These results need to be confirmed in an adequate series of patients.



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Quality Assurance on F^{18} production: Experience with GE II target/ion source system for the minitracer cyclotron

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Introduction: Ever since the demonstration of FDG/PET in the diagnosis of cancer and in target delinearation for radiation treatment, major medical centers as well as oncological centers across the world are including FDG/PET as one of their premium imaging modalities in cancer care. Due to the relatively short half-life of positron emitting isotopes, a good number of centers have been adding small compact medical cycletrons into their practice to generate FDG as well as other tracers for research purpose.

To meet the demands of more than 6000 FDG studies a year plus additional research projects on oncological imaging using new F^{18} tracers and PET/CT, the North Florida Cycletron Center USA, a division of the Integrated Community of Oncology Network (ICON) in Jacksonville, Florida, recently upgraded their ion source and target system to boost its F^{18} production with inhouse GE MiniTracer cyclotron. This upgrade is based on the GE Gen II target system as well as a new ion source that is capable of generating higher initial ion current and a target assembly that not only increases the target (H_2O^{18}) volume 50% from 1.3 mL to 2.0 mL but also increases the cooling capacity that allows higher target current from 35 μA to 50 μA. This combination allows more than 200% F^{18} production as well as FDG yield. In this paper, we describe a quality assurance (QA) program specifically designed for consistent F^{18} production.

Methodology: The process of FDG production has been compartmentized into three different parts. Part 1 involves the production of proton beams (target current) for the $O^{18}(p,n)F^{18}$ reaction. Part 2 involves the production of F^{18}, which includes the Oxygen-18 water target system, and Part 3 involves the production of FDG, which includes all the processes inside the FDG synthesis box. The performances with respect to each part can thus be assessed separately.

The performance of each cyclotron ran is analyzed based on the recorded log file. The mean and standard deviation of each operational parameter during the run were obtained. In addition, several indices specifically related to the quality of proton beams were derived for specific QA purposes; i.e. efficiency, symmetry, and convergence. Efficiency is defined as the ratio of the final mean target current to the respective mean of initial ion current. Symmetry is defined as the ratio of the mean of the right collimator current to the mean of the left collimator current. Convergence is defined as the ratio of the mean target current to the sum of the mean right and the mean left collimators and target currents.

Results: Fig. 1 illustrates the ion source current during a typical, smooth cyclotron run whereas Fig. 2 illustrates the same current but during a problematic run. The target current was preset at 50 μA for both runs. The differences between the two runs were that one was after the cathode and anode replacement, and the other one was prior to the replacement. To ensure a fixed F^{18} production at the end of the cyclotron run, the target current is always preset and maintained during the run. As a result, a feedback system is always in place to fine-tune the ion source current such that target current will continue to stay at the preset level. Information regarding the IS current during each run should shed some light as to how the cyclotron is doing from day to day. Before the replacement of anode and cathode, the IS current varied a great deal from one run to another; after the replacement, the IS current is much more stable. It is very puzzling that the F^{18} production was substantially lower than normal before the replacement, even though the target current was kept at 50uA. Neither the

Symmetry nor the Convergence Index was affected much by the problem on the cyclotron and the Efficiency Index may be the most sensitive index among them. The index correlates very well with the F^{18} production at the end of each run. The deterioration of the efficiency index may serve as the index to use to alarm the need for IS maintenance.

Conclusion and Discussion: A FDG production facility centered on a small medical cyclotron may not have the adequate supporting personnel that major or commercial FDG production facilities may have to keep the cyclotron running at all times. It thus relies on regular preventive maintenance to ensure consistent FDG production. However, there were numerous times when we experienced low FDG yields that relied on the FDG from a commercial facility. Through dividing up the process as well as tracking important operational indices such as efficiency, we think that we are capable of having better control over FDG production.

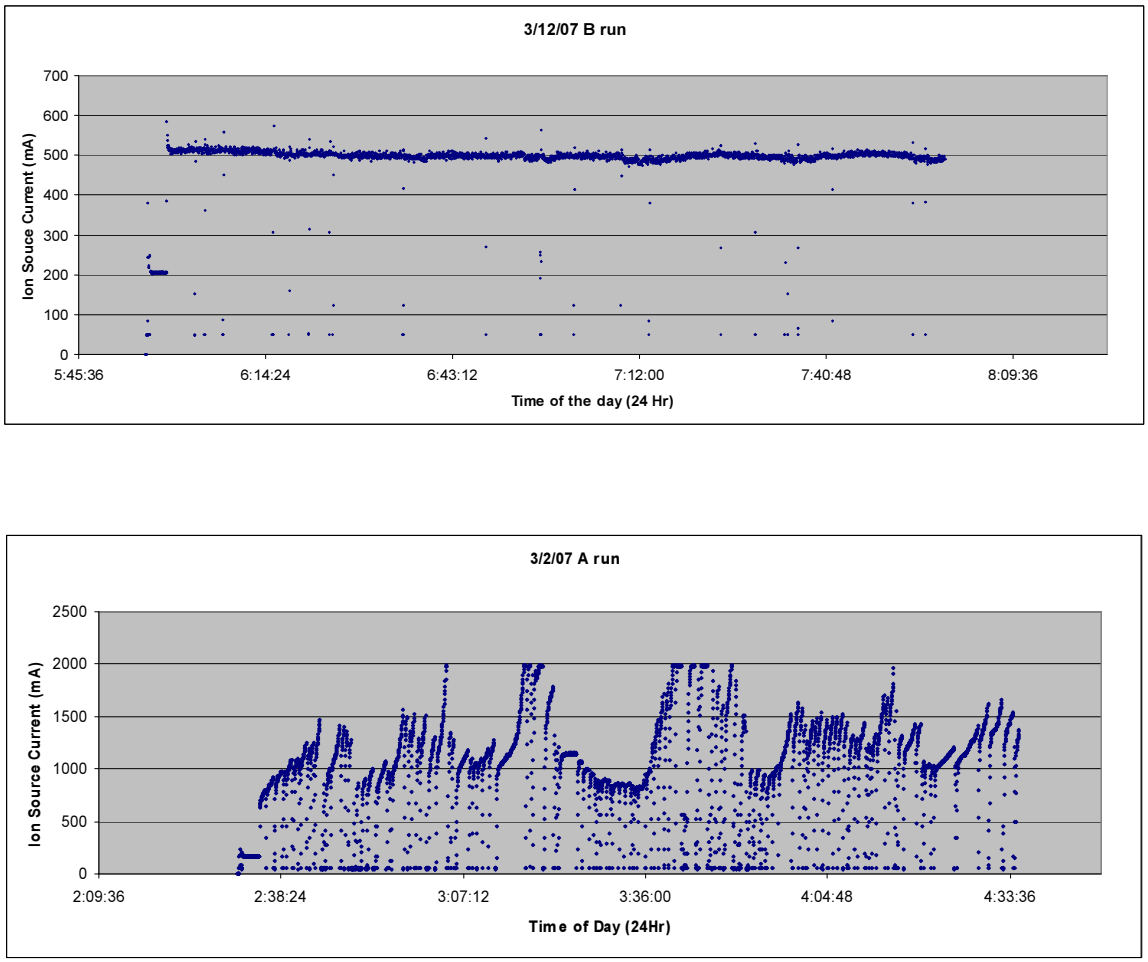

FIG. 1.+2. Ion source current vs time.

Measurement of muscle and whole body (WB) glucose metabolism (GM) in vivo by combined stable isotope (SI) and PET techniques - Validation in an animal model

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Aim/Background: Primed-constant infusion of SI labeled tracers is a classic technique for studying metabolism at the WB level, however, without invasive A-V difference data it provides no information about the metabolism of specific tissues. In contrast PET provides primarily tissue specific data. The aim of this study is to apply PET in combination with SI methods in an animal to simultaneously quantify substrate metabolism in specific tissues and the WB.

Methods and materials:
Animals: Seven white New Zealand rabbits (Mean ± SE 3.7 ± 0.1 kg;) were studied. After 14 hours of fast, they were surgically prepared by tracheotomy and implantation of catheters into carotid artery (Ca), jugular vein (Jv), and right femoral vein (Fv) under anesthesia.

PET Imaging: The animal was placed in supine position in the gantry of a PC-4096 PET camera. Transmission images (5 min.) with a rotating pin source containing ^{68}Ge were acquired with the central tomographic slice positioned to include both hind limbs (HLs). Each animal received $C^{15}O_2$ inhalation and was imaged for blood flow (BF) rate in HL muscles. Then, ^{18}FDG (~ 8 mCi) was injected into the animal through jugular vein, followed by serial PET images of muscle glucose metabolism (GM) for 90 min. Primed constant infusion of [6,6, $^2H_2$]-glucose (0.8μmol/kg/min, priming 64umol/kg) was conducted simultaneously. Plateau level blood samples were taken from the Ca and Fv for WB and HL GM.

Stable Isotope Measurements: The whole body glucose metabolic rate and the plasma glucose kinetics are calculated according to the conventional stable isotope steady state kinetics model.

$$Q = i\,(E_i / E_p - 1)$$

where i is the infusion rate of stable isotope labeled [6,6, $^2H_2$]-glucose, E_i and E_p are the isotopic enrichments of [6,6, $^2H_2$]-glucose in infusate and plasma under steady state conditions. The hind limb glucose metabolism was also measured using stable isotope tracer and tracee difference across the hind limb.

Results: SI measured metabolic parameters are shown in Table 1.

TABLE 1. GLUCOSE METABOLISM MEASURED IN WHOLE BODY AND HIND LIMB MEASURED USING STABLE ISOTOPES

Animal Number = 7	Unit	Mean ± SEM
Animal Weight	Kg	3.7 ± 0.1
Left Leg Weight	G	315.4±13.3
Left Leg Muscle	G	199.0±7.8
Whole Body Disappearance	mg/kg/min	2.54±0.22
Arterial Blood Glucose	mg/dl	210.3±17.7
Blood Clearance	ml/min	1.22±0.09
Leg Glucose Transport	mg/leg/m	0.77±0.12
Per Leg / Whole Body	%	7.63±1.14
Muscle Glucose uptake	μg/g muscle /m	3.40±0.46

WB GM determined by SI was 2.54 ± 0.22 mg/kg/min and GM in the right HL measured by A-V difference of SI was 0.77 ± 0.12 mg/leg/min. Based on muscle mass in HL (199 ± 7.8 g), LM GM (μg/g tissue/min) was calculated to be 3.40 ±0.46 by SI and 3.64 ± 0.22 by PET (N.S; paired t-test). BF to HL muscle determined by $C^{15}O_2$ inhalation was 0.059 ± 0.01 ml/g tissue/min.

Discussion: The two *in vivo* methods provided comparable quantitative information on muscle protein metabolism. PET measurements have the advantage of less invasive than A-V difference methods using SI, but it does not provide the information on whole body glucose disposal rate. Therefore combined SI and PET would provide more complete picture of whole body and regional glucose metabolism *in vivo.*

Conclusions: PET-SI is a non-invasive approach to simultaneously quantify WB and muscle GM without biopsy, hence a powerful tool for human studies under various physio-pathophysiological conditions.

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In vivo measurements of whole body (WB) and skeletal muscle glucose metabolism under basal and euglycemic insulin clamp (Clamp) by combined PET and stable isotope (SI) tracer studies

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Aim/Background: Primed-constant infusion of SI labeled tracers is a classic technique for studying metabolism at the WB level, however, this procedure provides no information about the metabolism of specific tissues. In contrast PET provides primarily tissue specific data. In this study, we combined PET with SI techniques to measure glucose metabolism in WB and lower limb skeletal muscle (LLM) of humans under Basal and Clamp conditions.

Methods and Materials: Four healthy volunteers (73.0 ± 6.0 kg, mean ± sem) were studied. After fasting overnight, each subject was injected with 10 mCi of ^{18}FDG and serial 1.0 min. PET images of the mid-thigh region were acquired over 90 min. Aterial blood samples were collected in parallel. Glucose metabolic rate (GM) was calculated with a 3-compartment / 4 rate constant model; LC assumed to be 1.0. A primed constant infusion of [6,6, $^{2}H_2$]glucose was performed in parallel with the PET measurements. On another day, the PET and SI measurements were repeated under clamp conditions. All results are expressed as mean ± sem.

Results: The glucose kinetics in whole body and in low limb skeletal muscles are shown in Table 1.

TABLE 1. GM IN WB AND GM IN WB AND DIFFERENT REGIONS OF LLM

Glucose Metabolism	Basal	EGIC
Anterior LLM (x10^{-3} mg/g/min)	1.65 ± 0.22	14.27 ± 3.01[a]
Posterior LLM (x10^{-3} mg/g/min)	1.55 ± 0.08	18.25 ± 1.81[a,b]
Average in LLM (x10^{-3} mg/g/min)	1.60 ± 0.15	16.07 ± 2.93[a]
Total GM in LLM (mg/LLM/min)	19.9 ± 1.2	211.0 ± 24.0[a]
GM in WB [mg/kg body weight/min]	1.85 ± 0.27	8.50 ± 0.78[a]
LLM / WB in GM (%)	15.6 ± 2.6	34.4 ± 3.0[a]

[a] $p < 0.001$ versus Basal
[b] $p < 0.02$ vs. posterior LLM

Under *in vivo* conditons, Clamp caused: 1) a 10.2 ± 2.3 fold increase in GM by LLM but only a 4.7 ± 0.4 fold increase in GM by MB. 2) Increaseed contribution of LLM to WB GM, indicating that LLM GM is more sensitive to insulin compared with anterior LLM (extensors).

Discussion: The study demonstrated the unique advantages of using PET to study substrate metabolism in specific tissues in human subjects:

i) It is less invasive than the conventional A-V difference and muscle biopsy method.

ii) It provides a more detailed picture of substrate metabolism in different parts of the muscle in the same limb, as compared to one spot muscle biopsy.Data in Table 1 demonstrated that GM in posterior LLM is more sensitive to insulin than that in anterior LLM.

iii) It can detect substrate metabolism in deep muscles which cannot be reached by biopsy technique.

Therefore PET combined with stable isotope tracer can non-invasively provide a more complete in vivo picture of glucose metabolism in WB and in different parts of the skeletal muscles in human subjects.

Conclusions:

1. Euglycemic insulin clamp (EGIC) caused a significant suppress of endogenous glucose production, either released from glycogenolysis or gluconeogenesis in the fasting condition.

2. Glucose metabolism in LLM is more sensitively regulated by insulin than other tissues.

3. On the same lower limb, glucose metabolism posterior muscle group is more sensitively regulated by insulin than those in the anterior.

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Basic requirements of quality control of PET radiopharmaceuticals

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Background/Aim: PET radiopharmaceutical (RPs) require efficient, simple, and well established quality control (QC) procedures due to short half lives of radionuclides (^{15}O: 120 sec; ^{13}N: 10 min, ^{11}C: 20 min, and ^{18}F: 110 min) used in their synthesis. Although QC procedures have been recommended by FDA, these are far from complete and quite often difficult to perform routinely due to limited time, resources, and lack of expertise. We have established basic guidelines of radiation safety and QC for the production of ^{18}F-dG and ^{18}F-DOPA for clinical applications (Sharma et al 2006). This report is to share basic knowledge of standard operating procedures (SOPs) and advanced procedures with well established and developing labs. It is expected that our experience will be beneficial and adopted for the successful and economical maintenance of PET-RPs labs.

Materials & Methods: SOPs were developed for checking temperature, pH, ionic concentrations, sterility, apyrogenicity, radiochemical purity, radionuclidic purity, and chemical purity. Mass spectroscopic procedure was developed for QC of PET-RPs with a special emphasis to 2-fluoro, 2-deoxy, D-glucose (^{18}FdG) as it is used extensively in clinical diagnosis.For compliance testing, NMR (^{1}H, ^{13}C, ^{19}F) and IR spectroscopic analyses were performed to check stability and shelf life of ^{18}FdG and mannose triflate. To determine molecular weight, purity, reproducibility, and shelf life, Bruker-BioToff Mass spectrometer was used. Inductively coupled plasma mass spectroscopic (ICP-MS) and graphite furnace atomic mass spectroscopic (GF-AAS) analyses were performed to estimate metal ion impurities of cyclotron targetry.

Results: We developed a simple, innovative, economical, and less time consuming mass spectroscopic procedure to determine chemical purity of PET-RPs. Overlay mass spectrograms of 37 production runs illustrating accuracy, sensitivity, reliability, and reprodicibility are presented in Fig. 1. The radio-HPLC and mass spectroscopic data provided a linear correlation which can be performed routinely, I.R, NMR and GF-AAS spectroscopic analyses can be performed for compliance testing. We determined bio-distribution of PET-RPs by microPET imaging using MicroPET Manager for data acquisition and AsiPro for image reconstruction in weaver mutant (wv/wv) and metallothioneins (MTs) gene manipulated mice. We developed protocols of noninvasive translational research for future drug development (Ebadi et al 2005; Sharma and Ebadi 2005; Ebadi and Sharma 2006; Sharma et al 2006a; Sharma et al 2006b; Sharma et al 2006c). Ethanol augmented cocaine and METH-induced reduction in striatal ^{18}F-DOPA uptake as seen in wv/wv mice. The striatal ^{18}F-DOPA uptake was also reduced in cocaine and METH intoxicated mice. A further reduction was observed when ethanol was co-administered along with cocaine.

Discussion: These SOPs are simple, economical, and efficient. The distinct advantage is that they can be performed onsite as well as offsite to determine shelf-life and stability of reagents and precursors, authenticate radio-HPLC-UV, radioscanning, and PET imaging data. These findings will be discussed in the IAEA meeting. It is envisaged that our experience and expertise will be of interest to clinicians, basic scientists, and radio-pharmacists.

Conclusions: These SOPs will facilitate novel PET-RPs discovery for early and differential diagnosis of neurodegenerative disorders, cardiovascular disorders, & cancer.

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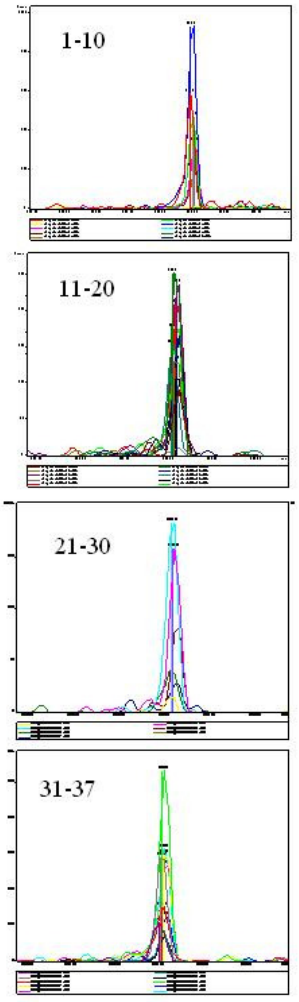

FIG. 1. Overlay mass spectrograms of 37 ^{18}FdG production runs. Temperature: ambient; Sample size: 5µl; Data acquisition: 50 seconds; Analysis time: 2 min.

Production of cyclotron produced radioisotopes in India

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India is harnessing the benefits of peaceful use of nuclear energy for past over 50 years. In the health care, reactor produced radiopharmaceuticals are routinely produced and used by the nuclear medicine centers in the country. The need for radiopharmaceuticals formulated from cyclotron produced radioisotopes was felt quite sometime back. India's first medical cyclotron for production of PET radiopharmaceuticals was installed in Mumbai in the year 2002 by the Department of Atomic Energy (DAE), Government of India. A few more similar (11-18 MeV) cyclotrons had been planned. After that three medical cyclotrons have become operational in India and five are in different stages of planning and construction including a 30 MeV cyclotron at Kolkata which is due to commence operation in early 2009. Out of the four PET cyclotrons which are operational in India, two are catering to the needs of the organization which house the cyclotron. The new 30 MeV Medical Cyclotron facility of the DAE coming up at Kolkata would be the first medium energy cyclotron in the country, primarily meant for routine production of SPECT radioisotopes like ^{201}Tl, ^{67}Ga, ^{123}I and ^{111}In to meet the demand of the entire nation. The facility would also produce the most important PET radioisotope i.e. ^{18}F. The cyclotron is planned to be used for research in other fields simultaneously.

This cyclotron being built by M/s Ion Beam Application (IBA), Belgium will be a 30 MeV (variable energy) proton machine and which will be able to deliver 500μA beam (maximum). The machine would have dual beam capability. Therefore, it would be possible to produce two different radioisotopes simultaneously in two beam lines. There would be a total of five beam lines. Four beam lines would be in the ground floor while the fifth one is taken into the basement. Three beam lines would be used for radioisotope production and the other two beam lines would be used for various research and development programme of the DAE. The ground floor layout of the cyclotron and target vaults is shown in the Figure 1. The facility would have state-of-the art processing equipment for production of the radiopharmaceuticals following guidelines of good manufacturing practice.

Entire package of radioisotope production and processing equipment including radioactive waste handling systems and safety equipment would be supplied by M/s IBA, Belgium and M/s Comecer, Italy.

Radiopharmaceuticals production and distribution would be done by a dedicated team associated with this project. In the first phase of the project three products, namely, [^{201}Tl]Thallous chloride, [^{67}Ga]Gallium citrate and [^{18}F]Fluorodeoxyglucose would be produced. [^{201}Tl]Thallous chloride and [^{67}Ga]Gallium citrate would be produced every week and distributed to the nuclear medicine centres in India. [^{18}F]Fluorodeoxy glucose would be produced daily and supplied to the nearby nuclear medicine centres. In addition to this, possibilities of exporting the SPECT radiopharmaceuticals to the neighbouring countries are being explored. Kolkata is located strategically in the eastern part of India. The facility will be well placed to supply cyclotron based radiopharmaceuticals to the entire south east Asia.

Soon after the commissioning of the facility for production of above mentioned three radiopharmaceutical, it is being planned to start production of useful radiopharmaceuticals of ^{123}I and ^{111}In. Moreover, depending on the demand, radioisotopes like ^{124}I,^{64}Cu, ^{186}Re, ^{68}Ge-^{68}Ga (generator) etc. could also be produced.

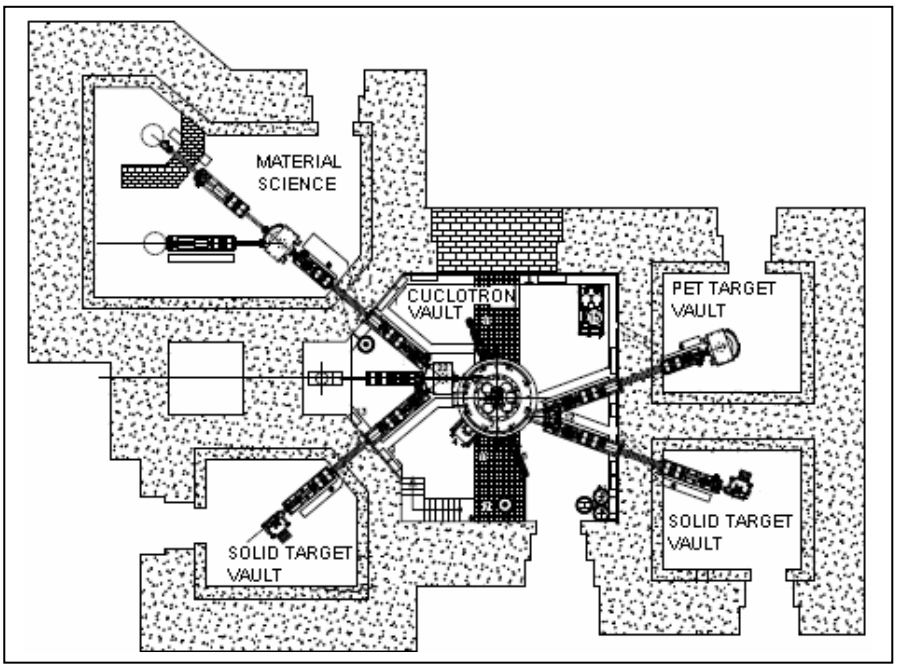

FIG. 1. Lay-out of 30 MeV medical cyclotron facilities at Kolkata.

POSTER SESSION IV

PHYSICS, RADIATION PROTECTION

Image fusion based on images of SPECT and CT modalities acquired in separated scanners

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Developing countries have several limitations to acquire the new high cost hybrid devices such as SPECT-CT or PET-CT for combined clinical diagnosis, due to the very limited budget most hospitals currently have.

However, the information that combined diagnostic modalities offer to physicians is very helpful in determining the exact site of radiopharmaceutical concentration both in physiological or pathological situations, leading to a more accurate treatment for patients. Moreover, the information obtained from the electronic density from X rays on CT images gives the information that radiologists need for morphologic diagnosis. In our experience combined imaging modalities (metabolic and structural) gives usually more information that the sum of individual modalities. This opinion is based on performing corregistered PET-CT imaging over thousands of patients.

In this paper, we propose an Acquisition Protocol to obtain SPECT and CT images from already existent dedicated devices in a hospital, in an appropriate condition allowing to be used for corregistration and later on, fusion and interpretation. Since the patient must move from one scanner to the other, we set the following conditions in both scanners:

- Planar bed, which is accomplished by putting an insert over the conventional bed. This append must have a very low attenuation correction, such as MDF, wood, polycarbonate, or glass fibber, strong enough to support the patient weight.

- Head and neck support, to fix head and neck, depending on the region studied.

- Thermoplastic mask fixed to the head and neck support, in the same way that is used for radiotherapy planning.

- Angle guide to place the patient's head in the most accurate position. This setting is also used in radiotherapy.

- Belts to properly fix arms and legs.

- Pillows, cushions and blankets to assure patients comfort, avoiding the risk of involuntary movements due to cramps and pain.

Depending on the clinical case under study, patient fixation may not be a limitation to acquire images from different modalities in separate scanners. The accuracy of patient positioning may not be crucial when skull or head is been studied, because it is a rigid region that makes corregistration of images really easy. That is not the case for the rest of the body, where the articulation between regions or even in the same region makes a rigid corregistration impossible, when repositioning the patient in the second scanner is not taken care of. With a good repositioning, a reasonable corregistration is feasible. Modern software for 3D elastic corregistration may improve certain inaccuracies on positioning while they are not important.

In our institution we use a Dual Head SPECT scanner, using conventional protocols depending on the tracer and the region studied. Typically, 60 to 120 frames with 30 to 60 second acquisition time per

frame, and different matrix sizes (64x64,128x128) are used in collecting nuclear medicine tomographic images. It's also possible to acquire images in a Single-head SPECT scintillation camera, using a specific number of frames, but taking care of the total acquisition time.

CT images are acquired on a helical CT, 1.5 pitch 0º tilt angle, 5 mm thickness, no interslice space. In several cases a retro reconstruction to 2.5 mm can be used.

Image corregistration and fusion are made on a Xeleris Workstation (GE), which allows to corregister different modalities, with a good display of fused images for clinical analysis. A second workstation running another software, which allows different automatic methods, was used and results were compared.

Clinical experience was obtained with patients with a facial tumor disease (using Tc^{99m} MDP as the radiopharmaceutical marker), patients with hepatic hemangioma suspected disease (using red cells labeled with ^{99m}Tc) and patients with pulmonary disease (using Ga^{67} as the radiopharmaceutical marker).

Results in the application of this protocol reveal the validity of the proposed method, allowing a complementary diagnose conducted by the application of the two image modalities.

From a physical point of view, the possibility of using CT images to correct for photon attenuation inside the patient (during the SPECT acquisition) is an additional feature to analyze in the whole result of the method. Attenuation image conversion because of changes in photon energy of the two modalities (140 keV photons of ^{99m}Tc for SPECT and 80 keV X ray in CT) is not straightforward, but efforts have been made to associate Hounsfield number values with specific tissues, for which there are tabulated values that relate different attenuation factors with different energies for each material (tissue). This final issue allows us to perform attenuation conversion.

The addition of an extra bed to fix thorax and lumbar regions as well as the legs, adds an extra attenuation that must be analyzed, and if it's the case, it must be taken into account in reconstruction procedures. This experiment is currently performed by our team.

Although this method requires very accurate work of different kinds of professionals, like technologists, physicians and physicists, when the protocol is applied in a "step-by-step" way, registration results obtained can attain an accuracy degree of almost one order less than similar studies acquired in SPECT-CT commercial scanners.

Using this Acquisition Protocol, a Diagnostic Imaging Center located in developing countries can perform diagnose studies with a higher content of information without the immediate need of acquire technology that is out of its economic scope.

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PET -TAC protocol acquisition for whole body corregistration

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Abstract: The development of this work consist of the implementation of Computer Axial and Positrons Emitted Tomography Acquisition Protocols using Fluordesoxiglucose (18F-FDG) to obtain images compatible with the registration as it is too sensitive to the patient position, breathing, observing pathology and election of adequate variables in the respective tomographs.

It was proved through the use of registration software that the application of protocols succeed in lining up images in a more useful and reliable way because outside the brain the corregistration is more dificult.In this way we try to improve the corregistration of imagenes with a prospective protocol of adquisition.

Background/Aim: Positrons Emitted Tomography (PET) it is the most advanced technique in Nuclear Medicine to generate metabolic images.With this technique hole body metabolic imagenes are generated.Clinical application in areas like the oncology determines the importance of the images corregistration with anatomical images generated with helical computed axial tomograph and nuclear magnetic resonance.

At the present time the denominated PET-CT acquire both groups of images simultaneously without moving the patient. In the centers in those this equipment are not available is necessary to acquire the images separately and then apply corregistration algorithms. These algorithms are very sensitive to the used protocol of acquisition which should be compatible with the registration software. This compatibility has been validated quantifying the errors on the patient's different structures.

Material & Methods: For this work it was used a PET Quest 250 UGM Medical System an Helical HiSpeed FX/*i* tomograph, and an Advantage workstation (General Electric).

We validate different protocols of adquisition using the root square mean error between anatomical landmarks.

The PET protocol consider all the clinical consideration to make a common hole body scan. Then the patient is inmovilizated with a Vac-lok with arms up for whole body scan and arms down for neck and head.After that the patient have to be located in the center of the FOV.The Vac-lok it is filled with tiny polystyrene beads. While semi-deflated, the cushion is easily molded around a patient’s anatomical contours then becomes a rigid and comfortable mold when a complete vacuum is drawn, offering accurate reproducibility of the positioning. A neck support is also used.After the patient is positioned laterals marks are made with the lasers of the PET tomograph. That marks are necesary to aling with the helical tomograph to reproduce the positioning.A protocol of acquisition of whole body is used. The number of frames varies according to the patient (maximum 7 frames), and the time programmed by each frame varies according to the activity, can be seven or five minutes by position of the table. A FOV of 512mm is used. The parameters for the acquisition of the emission are 4mm by slice,without space between slices. The trasmision parameters are also with a thickness of 4mm.

After the acquisition of the emission and transmission sinograms the reconstruction of the image of emission corrected by attenuation and the image of transmission are made with a matrix of 128 x 128.

For the TAC the patient must be relaxed.The size of the internals organs should be approximated (stomach, bladder).If it si necesary the paciente have to drink some water 30 minutes before the CT scan to have the bladder like the PET. For the positioning in the Helical tomograph was designed and adapter of curvature of the tables of the diferents tomographs. The adapter of curvature was made with

expanded polystyrene.With the scowtview we select the lenght of the hole body scan that it is the same as PET.The acquisition shoul be made in an helical mode.

The programming for the acquisition is made by groups. Several forms were implemented to apply those groups:

The first methodology is to obtain a corporal Scan of neck, thorax, abdomen and pelvis, programmed in a single group in the same series. In this stage the challenge is to handle the breathing of the patient to obtain approximate pulmonary volumes in each modalities; which is an average of the breathing in rest state. Several protocols of breathing were made. One, consist in take air and then expel it; the obtained result is a smaller pulmonary volume to the volume of PET. The other variant applied and the most approximated is a normal expiration and not to breath.But when the acquisitions is take in a single group the time of the scaning is about 50seg. This time is long, so is allowed to the patient to make and slow breathing when the tomograph scans abdomen and pelvis.

The second methodology is to make the acquisitions in several consecutive groups. First, the acquisition of neck, then thorax and in last time abdomen and pelvis. The breathing have to be similar between groups.The slice is of 7mm, pitch 2, tilt 0, 120Kv, tube current between 150 and 200 mA.

In the corregistation of the images we use the set of the CT images as reference and PET´s emission and transmission images are alining to the reference. First we align the transmission with the CT because we can identify lungs and some anatomical landmarks near the skin. PET´s images are fited to the FOV and to the size of the matrix of the CT images automatically by de software. After we load the images in the workstation we have to choose the landmarks for the alignment.

The corregistration can be rigid or plastic.The rigid corregistration consist in lineal transformations like rotations and translation.

For the validation of the protocols of acquisition three pairs of points are chosen at least.With that points we calculate the mean square error and after that we evaluate the results of the protocol of adquisition.

Result and Discussions: The studies that were acquired with the protocol were easy to corregistrate and validate.From a sample of 25 patients we obtain an error of de 9,18 mm $\pm$ 4mm in the corregistration. It is imposible to have less error than that because we have diferences between an study an other in time and space. In addition the use of Vac-Lok is very important for the inmovilization and positioning of the patient

Conclusions: With the validation of the PET -TAC protocol acquisition for whole body corregistration we found a better way to corregistrate the images with any software, having more compatible images for the corregistation. In adition, it was found and economic and easy way to repeat the positioning of the patients with Vac –Lok and the Lasers.

Fusion of PET and molecular biology: Combined assessment of quantitative dynamic PET data and gene array results using the GenePET software

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The combined assessment of data obtained by positron emission tomography and gene array techniques provide new capabilities for the interpretation of kinetic tracer studies. The correlative analysis of the data helps to detect dependencies of the kinetics of a radiotracer on gene expression. The development of new radiopharmaceuticals requires the knowledge of the enhanced expression of genes, especially genes controlling receptors and cell surface proteins. The GenePET program facilitates an interactive approach together with the use of key words to identify possible targets for new radiopharmaceuticals.

In order to enhance the accuracy of PET in colorectal tumors, other tracers besides F-18-Deoxyglucose (FDG) are needed. The analysis of gene chip data may help to search for new possible radiopharmaceuticals. We used the combined approach based on quantitative, dynamic PET data and gene array results in these tumors.

We perform dynamic PET examinations routinely in oncological patients, using a 28 frames protocol with decreasing frame length for a total of one hour. Seventeen patiens with a colorectal tumor were examined with FDG for staging prior to surgery. SUV´s were calculated for the tumor and normal colon and compartment as well as non-compartment analysis were applied to the dynamic data. Tumor specimen were obtained on surgery from the tumor as well as from normal colon and gene chip analysis was used to evaluate the specimen. Relative expression values (REV) were calculated for each gene from the expression data.

The GenePET software was used to analyse gene expression data and PET data side-by-side (Fig. 1). Generally, gene expression was enhanced by at least 25% in 24% of all probes. Global FDG uptake, as measured by SUV, was closely correlated with glucose transporters and hexokinase. K1 was correlated with VEGF-A and VEGF-B expression, while k3 was associated with genes involved in the proliferation cycle. Interestingly, the expression of the VEGF-B receptor was positively correlated with SUV. The expression of the KDR type III receptor kinase (VEGF-B receptor) was significantly enhanced in tumors. The maximum expression of the VEGF-B receptor was two times higher in tumors than in normal colon tissue, providing a possible aim for a new radiotracer. Currently we are evaluating the radiolabelling of ZM323881, an inhibitor of the KDR type III receptor tyrosine kinase. The G protein coupled receptor 49, involved in the signalling cascade, provided even a higher difference in gene expression for tumor and normal tissue (115 REV in tumors, 10 REV in normal colon tissue). We noted a four times higher expression of the gastrin releasing peptide receptor (GRPR) in the colorectal tumors as compared to the normal colon. Based on these data, we initiated the use Ga-68-Bombesin additional to FDG in selected patients to detect an enhanced GRPR expression.

Gene chip data provide detailed information about the association of PET radiotracer kinetics and gene expression. The screening of gene chip data can help to identify new possible targets for radiopharmaceuticals.

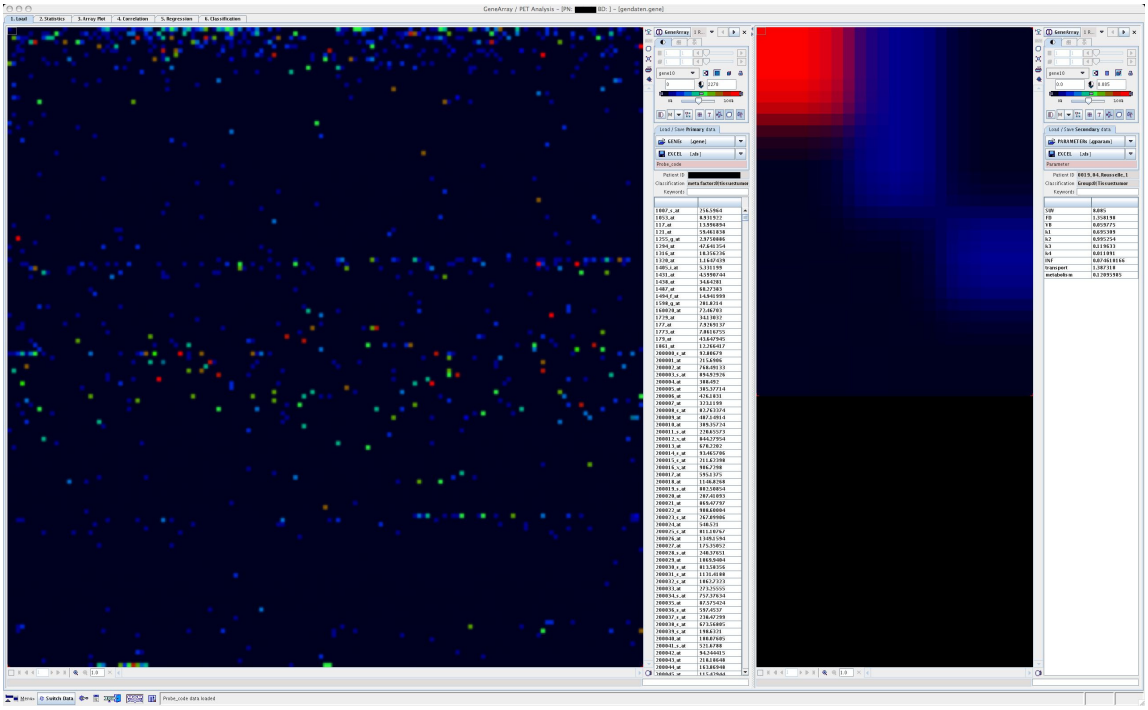

FIG. 1. Gene expression data (left) and quantitative PET data (right) are displayed as an image for the interactive, combined analysis of both methodologies. Gene probe values are expressed as REV and the expression values are displayed according to color and brightness for easy identification of enhanced gene expression.

Quantitative, dynamic PET for the detection and differentiation of bone lesions

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The role of the quantitative FDG-PET studies for the differentiation of benign and malignant bone lesions was investigated.

Methodology: The evaluation includes 116 patients. The FDG studies were accomplished as dynamic series for 60 min. The evaluation of the FDG kinetics was performed using the parameters: SUV, global influx, computation of the transport constants K1-k4 with consideration of the distribution volume (VB) according to a two-tissue compartment model, fractal dimension based on the box counting procedure (parameter for the inhomogeneity of the tumors). Molecular biological data based on gene arrays were available in some patients with giant cell tumors.

A two tissue compartment was fitted to the iteratively reconstructed dynamic PET data (Fig. 1). The mean SUV, the vascular fraction VB, K1 and k3 were higher in malignant tumors compared to benign lesions (t-test, $p<0.05$). While FDG SUV was helpful to differentiate benign and malignant tumors, there was some overlap, which limited the diagnostic accuracy. Based on the discriminant analysis, SUV alone showed a sensitivity of only 58%, a specificity of 90% and a diagnostic accuracy of 77%. The fractal dimension was slightly superior. The combination of SUV, fractal dimension, VB, K1 to k4 and global influx (Ki) revealed the best results with a sensitivity of 78%, a specificity of 96% and an accuracy of 89%. Bayesian analysis demonstrated true positive results at the level of 0.8 for a low prevalence of disease, if the full kinetic data are used in the evaluation. A limited comparison was possible with molecular biological data in patients with giant cell tumors. We noted primarily an association of PET compartment data with genes related to angiogenesis.

PET FDG has a good specificity for the exclusion of a malignant bone lesion. The evaluation of the full FDG kinetics and the application of discriminant analysis are recommended and can be used prospectively to classify a bone lesion into malignant or benign.

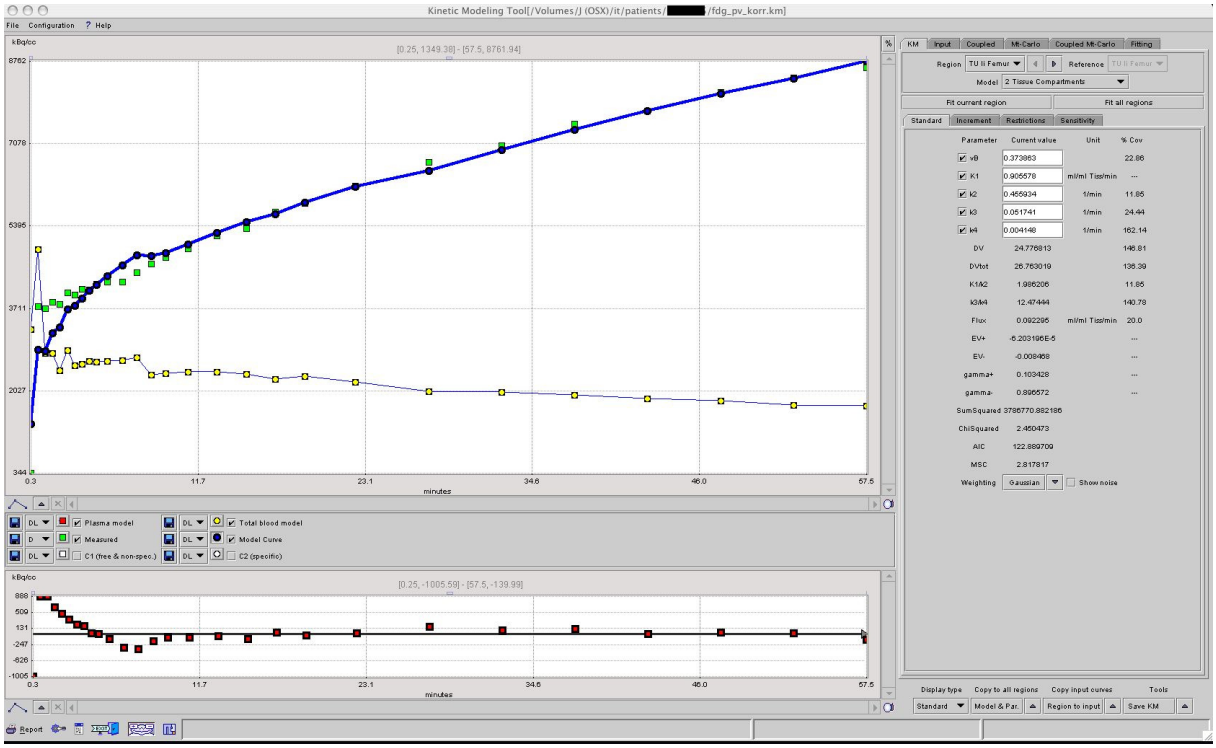

FIG. 1. Time-activity data for a giant cell tumor up to 60 min following FDG application. Bold line: time-activity data for the tumor; Thin line: time-activity data for the input function.

Hungarian experiences with PET/CT applications from a radiation protection point of view

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In Hungary PET examinations started about 10 years ago meanwhile PET/CT examinations have been carried out since 2005 with two new PET/CT centers and two medical accelerators (baby cyclotrons). The upcoming PET/CT applications represent the highest patient exposures in medical diagnostics with potentially the highest staff exposures as well.

The radiopharmaceutical, which is solely F-18 FDG in the actual Hungarian practice is transported in sealed ampoules in doses between 5-20 GBq. The dispensing of the doses and filling of the syringes are carried out in automatic dedicated hot cells. The glucose labelled with F-18 radioisotope (half life is 110 minutes) with a dose 370 MBq (for average patient) filled into a syringe is injected into a blood vessel of the patient. Then, the patient becomes the most significant radiation source of nuclear medicine. According to our measurements, the dose rates rise between 30-50 μSv/h at 1 m from the patient surface. The radiation is a very highly penetrating annihilation gamma radiation with an energy of 511 keV. The appropriate level of shielding needed should be determined amongst the active patients (two are waiting for examination, one is examined, 1 or 2 are waiting after examination) and the members of the staff and the inactive environment. The task is an optimalisation process, since the reasonable value of dose constraint should be decided.

For lack of relevant national regulation, it is the task of our Institute to determine the appropriate radiation protection requirements for the PET/CT centers. One of the two new Centers started in 2005 has been surveyed for months. Altogether 1092 measurements were carried out. On the base of measurements, it is proven that 1 mSv/year effective dose can be introduced as dose constraint for each separable source of exposures to the staff, namely for the administration of the radiopharmaceuticals, the radiation of active patients and the PET/CT examination. The requirement of dose constraint can be fulfilled if 15-20 cm thick normal concrete walls are built around the active areas. The shielding of the doors and the lead equivalency of the lead glass between the examination and operator rooms should be planned against CT radiation only (1.5mm Pb and 2.2mm Pb_{ekv} respectively).

Quality control and quality assurance in radiation medicine in the Republic of Moldova

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Quality Health care results from translating fundamental bench discoveries and making them available to patients. During the past decade, "molecular imaging" has emerged both as a new tool/technology and as a research and clinical discipline. Molecular imaging is an interdisciplinary approach involving biologist, physicist, physicians, mathematicians, radio chemists and other specialists who have joined forces for better understanding and visualizing of both normal physiological processes and the molecular processes preceding the morphological manifestations of disease in vivo / 2 /.

It is interesting to note, that despite major advances in imaging technology, cancer mortality has remained largely unchanged over the last three decades / 3 /. Imaging has thus far enabled us to look through a magnifying glass at disease processes but has failed to dramatically influence disease outcomes. Emerging data suggest that molecular PET imaging is about to change this situation.

Quality assurance is based on monitoring, measuring, evaluation, verification and recording of quantities, parameters and facts significant from the point of view of Radiation Protection. Quality assurance programs shall be established that provide, as appropriate: adequate assurance that the specified requirements relating to protection and safety are satisfied and quality control mechanisms and procedures for reviewing and assessing the overall effectiveness of protection and safety.

The Republic of Moldova with the support of the International Atomic Energy Agency perform the quality assurance and quality control procedures in the frame of the Technical Cooperation Regional Projects RER-6-012 "Quality Assurance and Quality Control in Radiation Oncology", and RER-6-011 "Thematic Program on Nuclear Medicine" / 1 /.

The Ministry of Health and Social Protection carry out the National Project "Ensuring Radiation Safety and Protection of the Patients" the principal goal being the Quality Assurance and Quality Control in Radiotherapy. In 2005 started the implementation of the National Project "Radiation Protection, Quality Assurance and Quality Control in the Nuclear Medicine".

Objectives of the Quality Assurance include: improvement in the quality of the diagnostic information, use of the minimum radionuclide activity that ensures the production of the desired diagnostic information, effective use of available resources. The quality of a practice is to fulfill the expectations and demands from the patient, the clinician, yourself.

The primary service of the Quality Assessment includes the communication with the client (patient, clinician). The final judge of any nuclear medicine practice is a clinical audit to determine the correctness and impact of the decisions made with respect to any method and process. e.g. internal audit, inspections by the Regulatory Authority.

Quality Assurance Program stipulate:

- Procedures i.e. patient history and signs, diagnostic question, appropriateness of investigation, contraindications;
- Planning of procedures (i.e. reliable administrative procedures, patient information, patient preparation);
- Clinical procedures (i.e. approved suppliers and materials, storage, preparation, clinical environment, patient handling and preparation, equipment performance, acquisition protocols, waste disposal);
- Data analysis (i.e. processing protocol, equipment performance, data accuracy and integrity);
- Reports (i.e. data, image review, results and further advice);
- Training and experience of nuclear medicine specialists, physicists and technologists and others involved;
- General outcomes (i.e. clinical outcome, medical exposure, patient satisfaction, referring physician satisfaction);
- Audits.

The Quality Assurance requests are the responsibility of the nuclear medicine specialist that the study requested by the referring physician is justified.
Special attention must be paid to studies requested for children and pregnant women. There Are alternative methods e.g. ultrasound, MRI etc.
Communication, on a regular basis, between the referring clinician and the nuclear medicine specialist is very important.
Very important problem of the Quality Assurance consist the protection of the patients which include:

- Identification of the patient;
- Information about the examination including premeditation;
- Waiting for the examination;
- An informed and motivated patient is the basis for a successful examination as well as staff who are well educated in care of the patient.

A procedure manual should be available for each type of study. The manual should be reviewed annually. Methods should be in accordance with accepted practices. Efficient use of computers can increase the sensitivity and specificity of an examination.
Diagnostic Report includes: patient identification, date and type of study, radiopharmaceutical and activity, study results - e.g. a graph or a series of images, objective description of findings, diagnostic conclusion and recommendations.
Registrants and licensees shall establish a comprehensive quality assurance program for medical exposures with the participation of appropriate qualified experts in the relevant fields, such as radio physics or radio pharmacy, taking into account the principles established by the WHO and the PAHO.
Quality assurance programs for medical exposures shall include:
- Measurements of the physical parameters of the radiation generators, imaging devices and irradiation installations at the time of commissioning and periodically thereafter;
- Verification of the appropriate physical and clinical factors used in patient diagnosis or treatment;
- Written records of relevant procedures and results;
- Verification of the appropriate calibration and conditions of operation of dosimetry and monitoring equipment; and
- As far as possible, regular and independent quality audit review of the quality assurance program for radiotherapy procedures.

Quality Assurance of the medical exposure include: choice of examination, determination of technical parameters, optimization of administered activity, methods of reducing the absorbed dose, quality control of equipment and radiopharmaceutical, quality assurance of methods, safe routines to avoid misadministration, quality control of radiopharmaceuticals, radionuclide purity, radiochemical purity, chemical purity, written and practiced procedures in preparation and safe handling of radiopharmaceuticals, use of a unique code which guarantees the ability to trace the origin of all components in the preparation, records of radionuclide, kits etc, labeling of vials and syringes.
Quality Assurance of the Occupational Exposure assume design of the facility, safe handling of unsealed sources, management of radioactive waste, safety equipment, personal monitoring, health surveillance, workplace monitoring, emergency procedures, local rules, training and experience of staff.
The main tasks of the **Quality Assurance** for radiotherapy include:

- Development of methodologies and procedures for acceptance testing and commissioning of radiotherapy equipment..
- Development of QA methods for radiotherapy dose calculations and computerized treatment planning systems.
- Provision of scientific and technical support to Member States for the development of quality control techniques and setting-up of national quality audit programmers.

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Software module development for high resolution PET systems

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Aim/Background: ClearPET is a small animal PET scanner device which is made by the CCC (Crystal Clear Collaboration) and used at the Juelich Research Center. A program based on IDL 6.1 (Interactive Data Language) named Module_Check written is aimed to be used for quality control of the ClearPET.

Methods and materials: The Module_Check program was written to evaluate the information which come from each module group and are stored in.ang files during the detection. In the program, the user shall input the address of the data. After that, the necessary graphs and outputs can be selected. Module_Check was tested with the ^{68}Ge and blank scan data acquired while the gantry was in fixed state, and ^{18}F, ^{68}Ge and blank scan data taken during gantry rotation. Maximum, minimum and average values and their standard deviations were found by program. Module_Check was tested whether or not it could find errors which were already known by checking ASCII formatted data manually.

Results: Graphics taken while the gantry was in fixed state was linear. Graphics of the ^{68}Ge and ^{18}F counts taken during gantry rotation was like sinus curve. Minimum and maximum angle values were observed at about 90° and 270° in these sinusoidal graphics. Averages of minimum and maximum angle values of ^{68}Ge counts were determined as 53°±15° and 227°±12°. Besides, averages of minimum and maximum angle values of module group counts taken with ^{18}F source were calculated as 246°±16° and 75°±16°. Counter to ^{68}Ge, minimum angle value was between 180°-270° and while maximum value was between 0°-90° in ^{18}F measurements. Blank scan measurement gives a noisy line though taken during gantry rotation. % deviation between minimum and maximum counts for rotating gantry was 16.9 for ^{68}Ge and 5.6 for ^{18}F. Additionally, the program found out that the measurements of Module Group 3 from 289th to 335th in ^{18}F experiment were inaccurate.

Discussions: This program can detect the errors. The program showed that Module Group 1 measurements were inaccurate for the blank scan data of in which error was known before. Additionally, the program found out that some measurements of Module Group 3 were inaccurate. This error wasn't known before the creation of the module group graphics.

Conclusions: Module_Check program runs correctly. This program may be suggested in order to use finding the errors of cassettes (module groups) of the ClearPET.

POSTER SESSION V

EMERGING PET PROGRAMMES

Experience of setting in operation a PET/CT-cyclotron facility in Argentina

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Recently, a new PET-Cyclotron facility has been built in Buenos Aires, Argentina. It consists mainly of a 11 MeV self-shielded cyclotron, a radiochemistry laboratory, a quality control laboratory and a state of the art PET-CT scanner.

In the current work we describe the diversity of issues which had to be addressed in order to set up in operation this facility in Argentina.

Since the PET market is still in its infancy in developing countries, local representatives of international vendors lack experience in providing adequate support during site planning, equipment installation and commissioning. Installation crews are mostly foreign, making scheduling of related tasks difficult and often fragmented due to overseas personnel availability.

Local nuclear regulations include PET-cyclotron facilities in the same category as a nuclear power plant, making nuclear safety requirements difficult to meet and add to increased installation and operation costs. In addition, personnel licensing and regulatory documentation generation are demanding processes in this context.

Harmonizing local clean-area codes with nuclear safety codes was also challenging since contradictions were often found between them.

Short Half-life radiopharmaceuticals in general and F18-FDG in particular are still not included in the Argentine Pharmacopeia, so quality control procedures are still in debate.

All the mentioned factors resulted in increased efforts and responsibility for the facility personnel and local contractors, adding to installation costs and completion time.

Prospect of PET-CT in a developing and transition economy like Bangladesh

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Background: Nuclear Medicine as a specialty has grown quite extensively in Bangladesh, yet its use in some areas is challenged due to the advent of other modern imaging modalities. Compared to advances in radiological techniques such as MRI and CT, which have successfully proliferated in Dhaka, the current Bangladesh scenario in Nuclear Medicine remains almost conventional. This is happening when all are keenly aware of the new dimension and direction of Nuclear Medicine especially after the introduction of PET and fusion imaging technology. The tremendous potential of PET technology has been realized in the developed world where 18F-FDG PET has been the fastest growing diagnostic modality in oncology in the past decade [1,2]. Further advances in molecular imaging have now given an altogether new definition to nuclear medicine. The question is whether this new capacity can be competently added to nuclear medicine in transition economies.

Aim: The aim of this presentation is to examine the feasibility of establishing PET-CT-Cyclotron centers in Bangladesh and to justify its use for clinical patient management and for research.

Materials and Method: Public and private Radiology and Nuclear Medicine centers in Dhaka were surveyed to analyze the current situation with regards to the presence of the latest state-of-the-art technology and the utilization of these services. Oncologists, cardiologists, neurologists and other key people were interviewed to assess the demand for advanced Nuclear Medicine Techniques and to determine the clinical feasibility of establishing PET-CT technology in Dhaka, Bangladesh.

Results: Diagnostic radiology facilities are available in all public and private hospitals with most centers having at least one 16 slice CT and a 1.5 Tesla MRI equipment. The only Utrafast 64-slice CT angio system is present in a large private hospital in Dhaka. Since its introduction in March, 2006 there has been remarkable response from the medical community with rapid adoption of the technique especially for cardiac investigations.

Nuclear medicine techniques for diagnosis, management and therapy in most diseases are well recognized by the medical community in Bangladesh. Both *in-vitro* and *in-vivo* services are offered by all the Nuclear Medicine centers in the country. In addition to conventional scintigraphy, therapy of differentiated thyroid cancer and hyperthyroid disorder forms the bulk of nuclear medicine services in almost all the centers. SPECT myocardial scintigraphy and SPECT neuroimaging are done routinely in a few more technically advanced nuclear medicine centers in Dhaka.

Clinical collaborations have helped to build multidisciplinary teams in areas of major interests such as endocrinology, cardiology, neurology and nephrology. Interactive discussions with different specialists reveal that there is much awareness of new and improved techniques that modern Nuclear Medicine can offer. Particularly the use of molecular imaging with positron-labeled ^{18}F-FDG is maintained to be in high demand in oncology. The pivotal role of PET in the staging of cancer, assessment of tumor response, selection or delineation of radiotherapy target volumes, detection of early recurrence, and as a tool to evaluate modifications in organ function as published in literature [3] are aspects that the clinical oncologist in Bangladesh aspires for in clinical practice. Further the potentialities of PET and hybrid imaging techniques in the evaluation and management of cardiac and neurological conditions are well recognized.

Discussion: In perspective of the many problems that plague developing nations such as disease, malnutrition, population stress, environmental degradation etc, one may argue against the validity of

incorporating the latest achievement of modern technology into these countries. However, it can also be reasonably assumed that any technology that will save life and help improve the quality of health care is totally not out of context.

In view of the ever-increasing trend of coronary artery disease and cancer in Bangladesh, the importance of incorporation of newer technologies to help improve patient management and enhance clinical outcome is keenly felt by various health care planners, institution and medical imaging community. Conversely, integration of new and advanced developments has relevance to technological evolution as a natural process when the time is right for crossing frontiers. There are many other objective and independent grounds to justify the establishment of PET and hybrid technology in developing and transition economies. In short, a country where modern radiology imaging like 64 slice CT and even functional MRI are successfully working, the potential for the use of PET-CT imaging is huge. Despite the higher initial installation cost, the returns are likely to be manifold.

Conclusion: Nuclear medicine has evolved over the years from simple functional scintigraphy to advanced molecular imaging providing valuable insights into the pathophysiology of the disease process which have never been possible before. This is of great advantage in the early diagnosis and adequate management of diseases. Especially in Bangladesh, another good reason is that the installation of PET-CT-Cyclotron technology will facilitate the achievement of the Millennium Development Goals in the country by substantially improving health care.

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Brazilian experience in the production of ^{18}F-FDG

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Positron emission tomography (PET) permits non-invasive use of radiolabelled molecular probes for imagine and assay in basically any biochemical process of cellular function in vivo. Despite a large number of radiopharmaceuticals for PET imaging, 2-[^{18}F]fluoro-2-deoxi-D-glucose (^{18}F-FDG) remains the most important radiopharmaceutical used routinely worldwide in clinical studies for oncology, cardiac and neurological application, as well as in basic research. The compound has provided a valuable tool for the study of the glucose metabolism in both normal and disease tissue.

The synthesis of ^{18}F-FDG is well described, achieved by a nucleophilic substitution reaction in automatic module available in the market for routine production. The main advantages of this method are the high purity final product, the reduced synthesis time and the decrease radiation exposition to the workers. The aim of this work is to describe the experience in the routine production and quality control of ^{18}F-FDG at IPEN-CNEN/SP, under GMP conditions

The $^{18}F^-$ is obtained by the nuclear reaction $^{18}O(p,n)^{18}F$ in Cyclone-30 (IBA), using enriched $H_2{}^{18}O$ (97%). To attend the demand and to increase ^{18}F- (fluoride) production yields, it was explored from the initial 2.0 mL silver target to 2.4 - 5.0 mL niobium target. In typical protons irradiation of 110-120 minutes, at energy of 18 MeV and current of 30 μA, about 98% of the activity was recovered in the QMA filter. At the end of bombardment, the fluoride is transferred directly to the automatic module (GE). All the reagents are with ultra-pure degree and provided as a “reagents kit” (ABX) that must be fit 15 - 20 minutes before the start of the synthesis. The whole synthesis takes about 28 minutes. The impurities are trapped automatically and the labeled precursor is washed away and sterilized by 0.22 μm Millipore filter. The resulting (16 ± 0.6) ml of ^{18}F-FDG is clear, colorless, neutral solution and it is dispensing in a sterile glass vial for further distributions doses. Thin layer chromatography tests are carried out for radiochemical and chemical determination, in TLC using acetonitrile: H_2O (95:5) and NH_4OH: MeOH (1:9) as solvents, respectively. Stability of ^{18}F-FDG is determined immediately and 10 hours at the end of synthesis (EOS). Sterility tests are performed by the microbiology procedures outlined in the pharmacopoeias in different culture medium. The apirogenicity is evaluated using the “in-vitro” Limulus test (LAL).

The activities obtained of ^{18}F-FDG, using the 2.0; 2.4 and 5.0 mL target and two automatic modules (GE) were 55,500; 88,245 and 256,817 MBq / batch and the yield of synthesis EOS varied among 40; 52 and 48%, respectively The radiochemical purity of ^{18}F-FDG were (99.04±0.96) % immediately and (95.91±4,09)% at 10 hours EOS. The Kryptofix level was below the detection limit of color spot test. Sterility and pyrogen tests were negative in all delivered vials. During the last year (2006), the Radiopharmacy Center has produced four times a week and distributed 7,335 doses at nuclear medicine services to several states of Brazil.

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Maintenance & operational aspects of medical cyclotron facility- Indian experience

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Background: The first Medical Cyclotron-PET Facility (MCF) in India was commissioned in Bhabha Atomic Research Centre, in 2002. The Facility has a GE-PETtrace unshielded cyclotron, support equipment for the cyclotron, automated PET-radiochemistry modules, QC-lab for PET-radiopharmaceuticals and a PET scanner. The cyclotron is installed in a 2-metre thick boronated-concrete vault with labyrinth access. The PETtrace accelerates H^- and D^- ions to give proton and deuteron beams of 16.5 Mev/75 μA and 8 MeV/60 μA, respectively.

The various sub-systems of cyclotron include, targetary, vacuum system, extraction system, water-cooling, and gas distribution station. The cyclotron vault is maintained at a negative pressure and the exhaust from the vault is released through a stack at ~50 metre height. The exhaust from the synthesis modules, which carries small amounts of short-lived radioactivity, are compressed in a specially designed waste gas system, installed in the vault, and allowed to decay before releasing through the same stack.

To ensure continued satisfactory performance, the cyclotron and its subsystems are maintained periodically by a team of engineers, physicists and chemists.

Materials & Methods: Preventive maintenance consists of: one day in a month shut-down for diagnostics and trouble shooting (minor-maintenance) and a two-week shut-down maintenance every six months (major-maintenance) when the cyclotron and subsystems are opened, cleaned and components susceptible to wear and tear changed. These include the Haver foils, He-pump diaphragm valve, extraction foils, vacuum pump oils, etc. The target, ion source, extraction foils, collimators, RF condiuts, gaskets, etc., are checked, cleaned and reassembled.

Since during operation, the scattered neutrons not only activate internal parts, causing localised high dose rates, but also sputter material leading to loose contamination within the tank. Well-documented and safe practices are followed during cleaning/maintenance and are carried out by trained personnel under Health Physicist cover. Removal of particulate material and loose surface radioactivity in the cyclotron vacuum chamber, Dees, RF-conductors, ion-source, collimators etc., is effectively done by utilising vacuum and the surfaces are swabbed with isopropyl alcohol. A dose rate survey around the vault is carried out and swabs are taken before personnel are allowed to remove breathing mask. All discarded materials are collected into plastic bags and marked as radioactive waste. The waste is discarded as per the regulatory guidelines safety rules once radioactivity comes to the permissible limits.

Except for the target and collimators, none of the other parts of the cyclotron are directly exposed to the beam. In addition, long-term contamination ($T_{½}$ varies from days to years) occurs in the accelerator chamber, target holder and auxiliary equipment. Cleaning and maintenance of these components requires a thorough understanding of radiation safety aspects.

Maintenance is completed by checking the various performance parameters and tuning done to optimize it.

Results: The minor and major maintenance schedules for trouble-shooting and preventive maintenance followed by us has been satisfactory and we have had over four years of satisfactory operation of the cyclotron with over 99.0% uptime. Shutdown due to component-failure has occurred only twice in this period.

Majority of the loose contamination comes from ^{22}Na produced by a complex but common reaction ($^{27}Al(p,3p,3n)^{22}Na$) from the deflector assembly, rather than ^{65}Zn from copper dees, or ^{60}Co from nickel in the stainless steel.

Discussion: Operations and maintenance of the cyclotron and its sub-systems are inter-related and a schedule is adhered to as suggested by the manufacturer.

The parameters such as beam energy (MeV), beam current (μA), energy spread, beam lines direction at target, maximum beam size, power density (W/cm^2) and heat generation in target during irradiation are some of the important operational parameters which need consideration. Beam density should be distributed over the target area (not focused as a point source) to avoid the damage to the Havar foil, whereas an off-center beam affects production yield significantly.

The production yield of radioisotope at the End of Bombardment (EOB) depends upon the beam current, target volume and irradiation time. Low current irradiation of target is desirable as it results in less wear and tear, hence, needing minimal target maintenance. A 2.2 ml high yield target and a 1.4 ml normal target are installed and can produce ~140 GBq and ~90 GBq of ^{18}F in 1 hour at beam current of 60 μA and 40 μA, respectively.

The facility is regularly supplying 35-45 patient doses of [F-18]-FDG to 5 different hospitals in Mumbai and so far 15500 patients, have already been benefited since its commissioning. About 65–80 GBq of [F-18]-FDG is synthesized daily with two dedicated synthesis modules.

Conclusion: The various operational problems, we have experienced over the last 4 years regarding cyclotron and subsystems' performance and solutions will be discussed in details. Being the first cyclotron facility in the country, its installation and operation has enabled a wealth of experience, which is now being shared with newer installations in the country and with IAEA fellows.

Feasibility study for PET - The right choice for establishing PET in emerging countries

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PET represents a new step forward in evaluating function of internal organs and has proven to be very useful in Oncology, Cardiology, Neurology and in the field of infection and inflammation.

In response to growing interest in the PET technology IAEA Department of the Technical Co-operation and the Institute of Pathophysiology and Nuclear Medicine from Skopje, Macedonia initiated a feasibility study for evaluation of local conditions for PET implementation in Macedonia as a part of the new project cycle (2007-2009)

This paper potentially will be contribute to the challenges of establishing PET in emerging countries, because Macedonia is a part of the Members States who are still in the planning stage of acquiring clinical PET.

For the purposes of this feasibility study, "Importance of establishing PET facilities in Republic of Macedonia" several options were evaluated, and the workframe were created.

The main points of this study are:

- to create a strategy for the provision of positron emission tomography in the country, including Basic principles of PET, Clinical application of PET and International status of PET;
- to evaluate the current status in Macedonia and relevant health statistics for the project;
- to indicate all recommendation for the further evaluation (technological and scientific issues, raw materials and supplier);
- economic evaluation of diagnostic imaging technologies, including price of PET and cost-effectiveness analysis;
- to analyze location, infrastructural and environmental conditions, work space, organization and overhead costs;
- to create the implementation scheduling and the budget for the project with financial analysis and investment evaluation;
- to see current problems and their solutions;
- to evaluate optimal clinical indications for PET imaging;
- to estimate reimbursement for PET.

Conclusion: the importance of this feasibility study is:

- to show the interest for the PET implementation in republic of Macedonia, because PET-s availability is still quite limited (the countries of East Europe/non member EU countries);
- to present all benefits for the country:

  1. PET has significantly impacted patient care and has proven to be a very cost-effective way to diagnose and stage diseases, especially in oncology.

  2. Cost-effective for a number of indication, despite the high cost of the equipment.

  3. One PET center per 2 million of population is recommended

  4. PET will contribute:

  - to develop and expend new diagnostic procedures in the country and in the region and to increase the quality of diagnostic procedures in the medicine in Macedonia;
  - to develop into center for PET imaging and production of PET radioisotopes (cyclotron produced short lived radioisotopes);
  - to establish production of short-lived radioisotopes for PET investigation needed for our country and open the possibility to supply other centers (potential consumers) with PET products;
  - collaborative research with the countries in the region;
  - to stimulate expansion of the PET technology in the region.

Establishing the first PET & cyclotron facility in Pakistan – Experiences of a third world country

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Aim/Background: The presentation is about the efforts and difficulties faced in introducing the idea of Pakistan's first ever medical PET Centre in a hospital environment.

The idea of PET & Cyclotron facility in the country was launched in 2001 as soon as the technology got clinical acceptance at international level. Approval of FDA and insurance cover for the imaging procedures helped in this regard.

The novel idea of having new and expensive PET technology in the country intrigued the technical personnel but was prohibitive for the financial managers. The initial budgetary estimate of establishing a PET-Cyclotron centre was nearly US$ 5.0 Million, enough to have a new Nuclear Medicine/Oncology Institute or ample for refurbishing the 2-3 existing facilities.

In year 2003-04 the idea was broached to the higher ups when presentations were held with the PET companies and their experts. Soon after this, an international Nuclear Medicine Conference held in Lahore provided an excellent chance to introduce the technology to a wider national audience. Participation and lectures by the ARCCNM experts was extremely helpful in this regard.

A feasibility study was performed locally in order to locate the best suitable place for the PET facility in the country. Institute of Nuclear Medicine & Oncology (INMOL), Lahore was chosen to have the Pakistan's first ever PET & Cyclotron facility. Financial and logistical support was gathered from Federal and Provincial governments.

Help of IAEA was sought in order to formulate the tender documents. It took almost a year to evaluate the technical and financial bids from various companies. The contract was finalized after 18 months of floating the tenders. The project is in execution phase now. A TC project from IAEA has enabled us to scramble technical assistance in various fields.

Conclusion: IAEA help is much required in performing a feasibility study and having technical support for Human Resource Development programme in countries where PET technology is still unavailable. In order to initiate, execute and sustain a productive PET& Cyclotron Facility, technical support from national and international fora is necessary.

Development of Russian's industrial and technological resources required to produce PET center equipment

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Positron emission tomography (PET) is one of the most sensitive and promising methods of nuclear medicine. During the last 10-15 years positron-emission tomography (PET) has developed into a routine clinical diagnostics approach used in oncology, cardiology, neurology, psychiatry and pharmacokinetics applications. Present broad application of PET is associated with the use of not only very short-lived “bio-isotopes”, but also of other, longer-lived positron emitters and generator systems.

At present, PET technique is becoming increasingly important in clinical functional diagnostics. Considering the growing demand from domestic medical institutions in PET diagnostic equipment, the task of providing the national clinics with such instruments becomes not only topical, but vital.

Although to present days major medical institutions in Moscow and in St. Petersburg have started procuring imported instruments for their PET, Russia’s industrial and technological resources required to produce PET center equipment are already enough developed. Research and development efforts that have been underway at Institute for Theoretical and Experimental Physics (ITEP), Efremov Scientific Research Institute of Electrophysical Apparatus (NIIEFA) with participation of Central Scientific Research Roentgen-Radiological Institute (CNIRRI) and Bakulev Cardiovascular Surgery Scientific Center (BCSSC) engendered a theoretical, technical and technological foundation for design and production of the equipment required to implement PET technique in the Russian clinical environment.

A several cyclotrons with target systems for PET-radionuclide production has been constructed and manufactured. The line of this cyclotrons including negative ion cyclotron CC-18/9 with vertical magnet and simultaneous dual beam extraction for accelerating 18 MeV protons 100 μA extracted beam current and 9 MeV deuterons 50 μA extracted beam current and negative ion cyclotron CC-12 with vertical magnet and simultaneous dual beam extraction for accelerating 12 MeV protons 100 μA extracted beam current.

Set of units for radiochemical laboratories of PET-centers has been manufactured and put in operation for automated radiochemical production of compounds and radiopharmaceuticals labeled by PET-radionuclides. The set include modules for the synthesis of ^{11}C-fatty acids, of ^{11}C-methylation tracers, of ^{18}F-FDG and ^{13}N-ammonium. Two types of shielding boxes for putting up radiochemical modules have been constructed and manufactured too.

A full automated Rb-82 generator infusion system has been constructed. Rb-82 generator system provides bolus and continuous injections under computer control with display output of all required current information.

At the 90 years last century experimental specimen of a full-body PET-scanner has been designed and manufactured in ITEP. This scanner comprises two half-rings with 9x18x30 mm bismuth germanate detectors housed in a circle of 1080 mm radius. From December 2005 design of high resolution PET-scanner for animal experimental investigations was started in collaboration ITEP and NIIEFA. This scanner will comprise three rings with the arrays of LYSO detectors. The arrays has 11 x 11 elements with pixels 1.6 x1.6 x 10 mm. PET-scanner will be manufactured and put in run in 2007.

In Fig.1 presented equipments, what is producing in Russia for PET-centers now.

Complex of technical and clinical trials of presented above units have been done. Two cyclotrons CC-18 put in operation in Turku (Finland) and CNIRRI (S.-Peterburg, Russia). Cyclotron CC-12 is under construction now. Set of radiochemical modules now put in ran at CNIRRI and BCSSC and use for clinical investigations more then one thousand of patients. Nine shielding boxes are using in PET-center CNIRRI now. The Rb-82 generator system have passed integration engineering tests. The system operates reliably within the designed specifications. Now Rb-82 generator system under validation procedure in Miami, USA.

Technical parameters and clinical result of using of Russian's PET technique are corresponding world-level analogous equipments.

Cyclotron CC-18/9

Rb-82 Generator System

Radiochemical system for synthesis labeling compounds

Shielding mini-box

FIG. 1 Equipments, what is producing in Russia for PET-centers.

Positron emission tomography and related technology in Latin-America: Current situation, prospects, and needs

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Introduction: The World Health Organization estimates that about 84 million people will die of cancer in the next 10 years if the current trend is maintained. More than 70% of all these deaths occur in low and middle income countries, where resources available for prevention, diagnosis and treatment are sometimes very limited. Cancer is one of Latin America's major killers, and many of its victims are dying unnecessarily because the disease is not addressed comprehensively. Many patients could be treated and even cured with early detection, accurate staging, appropriate selection of treatment modalities, and objective treatment evaluation. Properly trained human resources and cost-effective technologies are needed to fight cancer, with PET being one such technology. In spite of the high costs involved, the number of PET, PET/CT and cyclotron installations has been increasing in Latin-America during the past few years, making these important tools more available for the general population. The aim of this study was to present updated information about the status of PET and related technologies (PET/CT, cyclotron) in the Latin-American region.

Methods: We performed a survey using a simple spreadsheet containing the requested items to be filled in (instrument, institution/city, manufacturer/model, year of installation). Information was also requested on advanced projects for the next 5 years. The form was sent by e-mail to previously identified key persons according to their professional standing in the following countries: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela. In some cases such as Argentina, Brazil and Mexico, the survey material was sent to more than one person due to the size of the country and the expected difficulties for gathering complete data. A 5-point score to express training and educational needs for several professional categories and a few lines for comments were also included in the survey. All the returned spreadsheets were then analyzed, checked for duplication of data, and the contents grouped into categories.

Results: Results of the survey are listed in Table 1. Brazil is the country with the largest number of installed PET and PET/CT facilities, followed by Mexico and Argentina. However, considering the country population Chile has the best relationship with one instrument (PET or PET/CT) every 8 million inhabitants, followed by Venezuela (1 / 9,2 million) and Argentina (1 / 9,7 million). Most units are in the private sector, and the number of PET, PET/CT and cyclotron sites will practically double in the next few years according to existing projects. Training and education were assigned a high priority, with a need for education of referring physicians and the general public being rated highest, followed by training of technologists, nuclear medicine physicians, and radiologists. Many additonal comments sate that many health systems still do not accept coverage of PET procedures, and most governments seem very reluctant to invest on this technology.

TABLE 1. CURRENT INSTALLATIONS AND ADVANCED PROJECTS IN EACH COUNTRY (COUNTRIES NOT LISTED HAVE NO INSTALLED INSTRUMENTS AND NO FORMAL PROJECTS UNDERWAY)

Country	PET		PET/CT		Cyclotron	
	Installed	Projects	Installed	Projects	Installed	Projects
Argentina	3	5	1	4	2	2
Brazil	2	0	10	4	2	3
Chile	1	0	1	1	1	0
Colombia	0	0	1	1	1	1
Ecuador	0	0	0	2	0	1
Mexico	0	1	9	3	3	0
Peru	0	0	0	1	0	1
Uruguay	0	0	0	2	0	1
Venezuela	0	0	3	2	1	1
TOTAL	**6**	**6**	**25**	**20**	**10**	**10**

Discussion: The introduction of PET and PET/CT systems has expanded the availability of this tecnology in many countries of the region, with more than 30 existing facilities and a similar number to be installed during the next 1-5 years. However, some difficulties for a more extensive growth of this modality have been identified. Team work of medical specialists and managers is needed to locally demonstrate that PET technology is cost-effective and helps to develop a more rationale approach to patient care, thus optimizing available economic resources. Coverage by insurance companies and other type of health systems is also crucial for the viability and sustainability of PET projects in the region. Mexico is one such a case where the rapid spread of PET technology has been made possible by insurance coverage. Installation of a PET/cyclotron unit may have a significant impact among the local scientific community in a developing country. Beyond specific applications in health care, this technology represents an opportunity for on-site training of basic scientists, physicians, and technologists. Universities, private institutions, commercial companies and some international organizations should play a synergic role on this regard, under the catalytic influence of national and international nuclear medicine societies and organizations, including the IAEA. An increasing involvement of the IAEA could facilitate the dissemination of PET technology in the Latin-American region, as it has been successfully happening with other nuclear medicine modalities.

ACKNOWLEDGEMENTS

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A window on Greece (experience, present state of PT/CT scan facilities and reimbursement policy)

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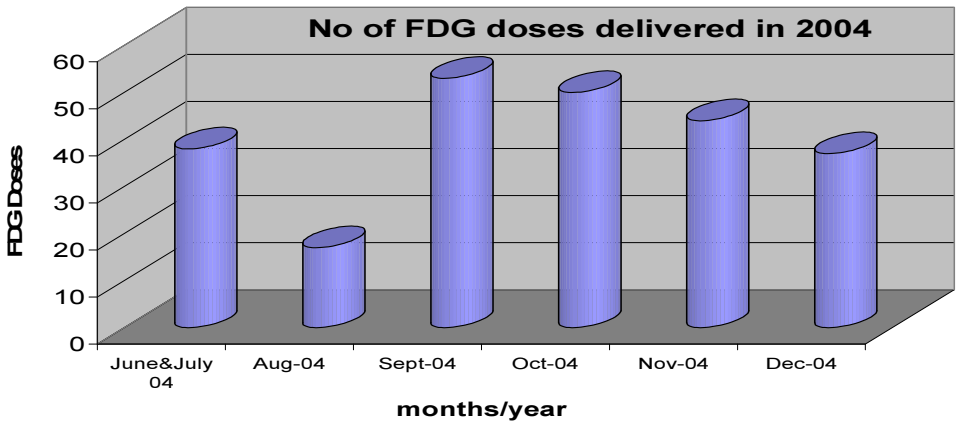
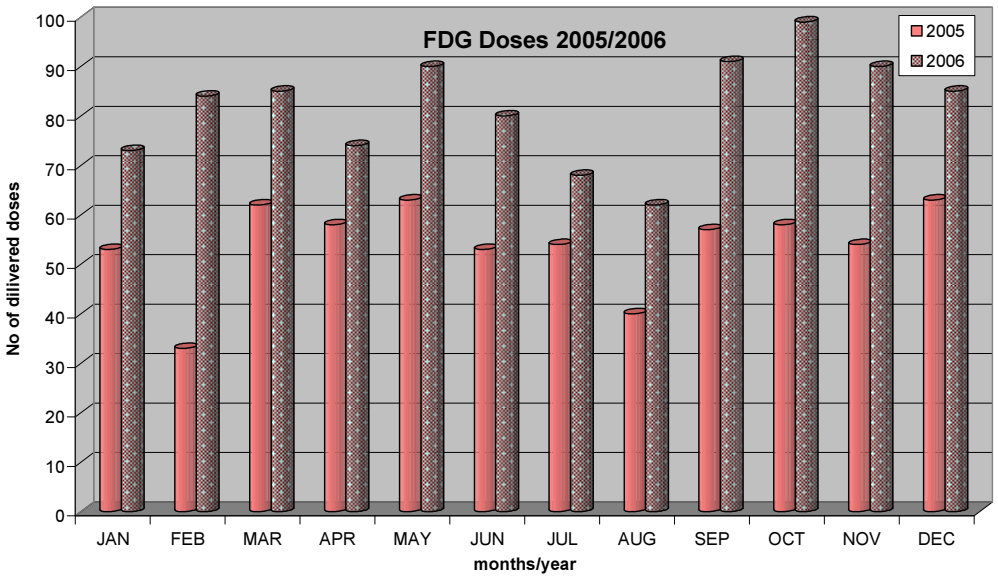
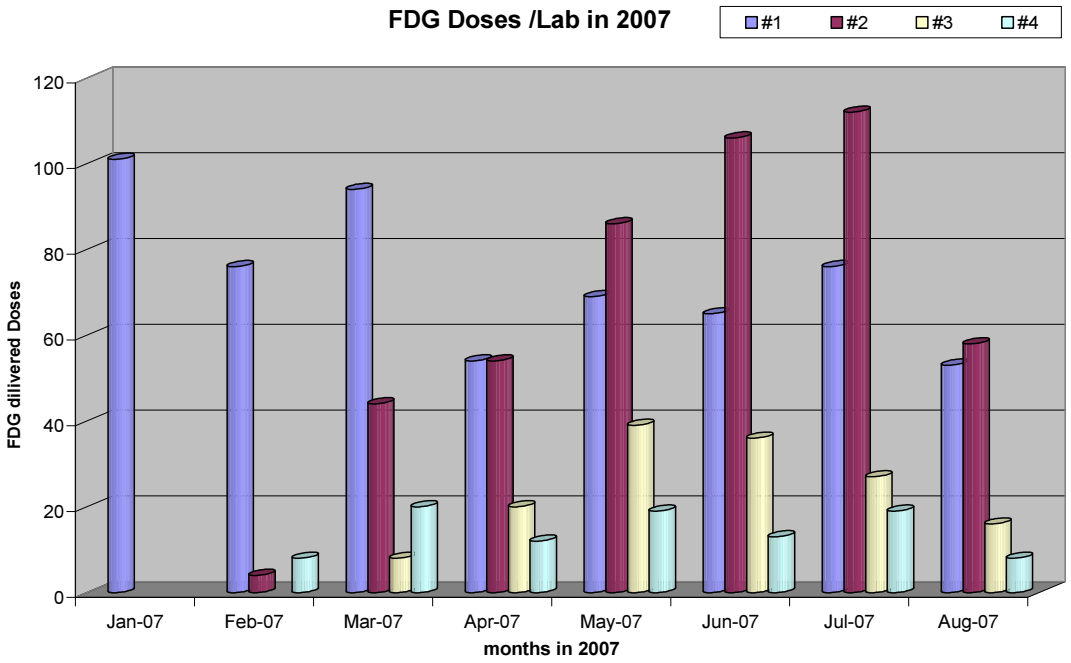
Development of Positron-Emission-Tomography (PET) dates back to mid 70ies albeit this imaging procedure gained its diagnostic importance not before 1990. Meanwhile, a lot of inventions occurred dealing with the software of the Positron-Emission-Tomographs as a necessity to cover the lack of detailed anatomy in the emission data. PET-CT systems have been manufactured and the edited fusion hybrid PET/CT morpho-metabolic images provide excellent high resolution stereotactic anatomical information.

The high popularity of PET/CT worldwide led to an improved situation regarding its cost reimbursement. Under this aspect the Greek Government and the Health Care System accepted, after a well documented medical report by the ordering physician, to cover the cost of PET/CT examination with **900 euro for the procedure plus the cost of any radiopharmaceutical** used (i.e. F-18 DG etc). Eleven consessions of PET/CT expendiencies, 7 construction approvals and 4 PET/CT running licenses have been issued up to September 2007. A 16.5 MeV GE PETtrace cyclotron has been installed at Lavrion area, about 40km along the city of Athens, the Greek capital. In the year 2004 it has started providing positron emitting radiopharmaceuticals in limited quantities and for the time being only F18-DG is distributed. So far, F18-DG is exclusively used for tumor imaging and mapping. Four PET/CT facilities for medical diagnosis are operated in Greece, up to now. The profile of the PET/CT doses/studies conducted per year as long as this report is written is tabulated below:




FDG Doses 2005/2006
2005
2006
No of dillivered doses
0
10
20
30
40
50
60
70
80
90
100
JAN
FEB
MAR
APR
MAY
JUN
JUL
AUG
SEP
OCT
NOV
DEC
months/year


FDG Doses /Lab in 2007
#1
#2
#3
#4
FDG dilivered Doses
0
20
40
60
80
100
120
Jan-07
Feb-07
Mar-07
Apr-07
May-07
Jun-07
Jul-07
Aug-07
months in 2007

POSTER SESSION VI

TRAINING & EDUCATION

Quality control and learning experience in clinical nuclear cardiology at a teaching hospital facility

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Introduction: Traditional Nuclear Medicine training includes seminars, guided practices and self-learning modules (continuing education and internet-based). We have developed recently a combination of training, quality control and active clinical research, with postgraduate nuclear medicine residents and pregraduate technology students. Goal: a) to assess the reproducibility of diverse techniques, among staff specialists and residents; and b) software application quality control. This, also in order to accomplish international parameters, mainly in nuclear cardiology training [1].

Methodology and Results: Four main cardiovascular subjects were selected:

A) Reproducibility in Lung V/Q Scans Interpretation [2]

401 studies from 382 patients with a possible pulmonary embolism were analyzed retrospectively; a blind lecture was performed by 6 independent observers with different experience level. Interpretation was based on individual experience and revised PIOPED criteria. Original reports included 27.2% high probability and 67.3% low probability. Interobserver agreement range was: 73-86% and correlation with original report: 74-82%. Excellent interobserver concordance and *kappa* was found, higher in experienced observers.

B) Perfusion SPECT in Coronary Artery Disease (CAD) [3]

60 cases with recent myocardial infarction with successful thrombolysis were blindly interpretated by 2 independent specialists and also by 5 in-training observers from different universities. Excellent interobserver agreement was obtained by specialists for normal/abnormal perfusion and wall motion (98.3% and 93.3%, respectively). Agreement between perfusion and wall motion was adequate, as well as assigned artery analysis. There was good correlation interpreting myocardial perfusion SPECT at both centers, with better adjustment in more experienced observers.

Currently, we are developping another study comparing interobserver reproducibility for exercise electrocardiogram and perfusion images including 100 known and unknown CAD patients. Four (local and IAEA) different experienced residents interpretations are compared to both specialist's report.

C) Reproducibility of Myocardial Spect with Artifacts [4,5]

Patient motion and extracardiac tracer activity may affect myocardial perfusion SPECT interpretation in CAD assessment. Interpretation changes after applying motion correction software, as well as reproducibility of automated functional parameters in presence of extracardiac activity (intestinal loops or liver) were analyzed.

C.1. Motion Correction: 160 selected CAD ^{99m}Tc- sestamibi studies processed with automatic and manual motion correction were divided according to presence of i) motion severity during standard acquisition and ii) perfusion defects. Motion correction must be used with caution to optimize myocardial perfusion SPECT CAD specificity. It's use must be decided according to individual performance. Cases with severe motion should be repeated due to variable results.

C.2. Extracardiac Activity: 100 ^{99m}Tc-Sestamibi- Dipyridamol studies, 50 with and 50 without extracardiac activity; each included 25 with and 25 without perfusion abnormalities. They were processed automatically and by 4 independent operators with commercial software. Extracardiac

activity affected automatic *QGS-QPS* assessment, even with manual intervention. Reproducibility worsened when significant activity was close to the myocardium. Perfusion abnormalities did not interfere with reproducibility. It was higher for functional than for perfusion parameters.

D) Reproducibility in Planar and SPECT Radionuclide Angiography [6,7]

83 radionuclide angiography using labelled ^{99m} Tc-red cells were classified according to ventricular dilation, wall motion abnormalities and systolic dysfunction. Both ventricular ejection fraction and volumes were obtained using available software for planar and SPECT. Good correlation existed between SPECT and planar studies for left ejection fraction and volumes. SPECT was useful in cases with functional abnormalities, however, was less reliable with smaller cavities. Excellent interoperator reproducibility for both techniques was observed, better for left ventricle.

Conclusions: This academic task performed during the last 3 years -accomplished using local databases and daily routine exams- was mainly a practical training for our nuclear medicine residents in order to ammeliorate self-confidence in the interpretation. Less frequently performed techniques were also reviewed this way.

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Training management at establishing a PET/CT service in a country with limited economic resources

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Training itself, and management of the training process are key factors for successful establishment of PET/CT service. In countries with limited economic resources training management is of particular relevance due to the absence of respective local reference centers in most of the cases. After having successfully established the first PET/CT service in the Baltic States during the period of 2002-2007 we would like to share our experience and to discuss our mistakes and success, in order to provide some hints for colleagues from the countries with similar state of economy.

Our current experience demonstrates that training management became a big challenge, addressing simultaneously two very conservative areas in terms of change management – healthcare and education. Accordingly, learning and training of managerial skills was the first lesson in this process. In 1999 we established cooperation with MIR, the subcommittee on Management of the European Society of Radiology. MIR provides a forum for education and exchange of ideas and state of the art concepts on imaging management aimed at enhancing the contribution of imaging to medicine. MIR addresses not only core managerial issues, but also supportive methods and techniques, especially information and communication.

As a rule, imaging staff is treated as main target for training activities at establishing PET/CT, while clinical evidence is regarded as the most important content of the educational activities. Our experience is supporting these considerations. However, besides the imaging personnel, there are numerous target groups with specific training needs whom one should never forget.

In our case, separate training strategy was created for each of the following target groups: a) health care managers; b) clinical partners of the imaging department; c) radiation safety specialists; d) staff of logistics and transportation; e) patients; f) health insurance; g) nuclear medicine technicians; h) physicians performing PET/CT studies (separate strategy for nuclear medicine physicians and for radiologists). At the initial stage we did not identify radiopharmacists as a separate target group, because we were relying on commercially available 18-F-FDG. At the present, the importance of this group is very well recognized.

At the beginning of the process training was focused on justification of the method. At this stage the dissemination of evidence based knowledge about clinical indications for PET studies was most critical. In our case we realized that clinical partners were not necessarily aware about the most recent developments in the field of nuclear medicine. If this would have been ignored, inappropriate attitudes towards the new techniques would have been appeared and we would never been able to establish the service. Training made clinical partners our allies.

In our opinion, in countries with limited economic resources the main problem is not the ‘absence’ of financial resources, but the lack of ability to release the resources for evident needs. In such circumstances training has to demonstrate which of the existing problems every target group may get solved. This is very essential for getting sufficient amount of money for the PET-project. On the other hand, the amount of required financial resources strongly depends on the level of skills of the technical staff involved into preparation of procurement documents.

As a multimodality technology, PET/CT sets new managerial challenges for the teamwork. According to the recent draft paper on relations between nuclear medicine and radiology, European Association of Nuclear Medicine (EANM) and European Society of Radiology emphasize the need for close cooperation in research, education and clinical practice. The same is valid for training of clinical partners on daily implementation of the PET/CT results.

At our centre we have used any available resources for systematic, individual or distant training of different target groups. In this regard, the inputs from the training activities of the IAEA (regional workshops, meetings etc.) have been extremely valuable. At the current stage we are looking forward to developing the collaboration with the IAEA in coming years. Training project on radiopharmacy, distant training for nuclear medicine technicians, training courses on PET/CT co-organized by IAEA and EANM, quality auditing of nuclear medicine facilities are just some examples for this cooperation.

In conclusion, we would like to emphasize that establishment of a PET/CT service is a big challenge in the field of training management, which should focus on different needs of different target groups. In countries with limited economic resources education is a pre-requisite for launching a PET-project. Properly managed training makes the process of establishment of PET/CT fast enough and in financial regard - lean enough in order to assure the success.

Cooperative learning in the modern era of PET imaging education and training: Philippine experience

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Aim/Background: Since the introduction of the PET Imaging Center of St. Luke's Medical Center in the Philippines last 2002, there have been cooperative efforts between local and international government agencies, hospital institutions, medical societies and organizations to promote PET Imaging and training in the country. This study aims to identify and elaborate the different educational methods used for the promotion, learning and training of PET Imaging in the modern era among nuclear medicine residents and physicians in the Philippine context. This study likewise discusses the participation of the different institutions and organizations in promoting PET Imaging Education and Training in the country.

Methods and Materials: This descriptive study consists the review and analysis of documents, interviews, surveys and brainstorming activities pertaining to the educational methodologies used for the promotion of PET Education and Training primarily among nuclear medicine residents and consultants in the Philippines. This study likewise involves the identification of strategies on how PET Imaging Education is incorporated in the nuclear medicine residency training programs among different institutions and how each cooperates to achieve this goal.

Results: Various educational processes were elucidated in the promotion of PET Imaging Education and Training in the Philippine context. This primarily involves cooperative learning methods among nuclear medicine residents in learning the principles of PET Imaging. In addition, different local and international organizations collaborated in promoting PET Imaging Education and Training in the Philippines through training and conference grants.

Discussion: Since the introduction of the PET Imaging Center of St. Luke's Medical Center, in the Philippines last 2002, there has been collaborative efforts between different hospital institutions to incorporate PET Imaging as a unit of instruction (i.e., rotations) in their Nuclear Medicine Residency Training Programs. Participating hospitals include (1) University of Santo Tomas Hospital, (2) Philippine Heart Center and (3) Cardinal Santos Medical Center. This "consortium" provides the nuclear medicine residents with the opportunity to participate in cooperative learning activities together with PET Imaging rotators from the host hospital. Learning activities which infuse cognitive knowledge in the field of PET Imaging include interactive case discussions, peer-review of journals dedicated to PET Imaging and case conferences coupled by post-rotation evaluation/feedback tools. This rotation grooms the nuclear medicine residents for familiarity with PET Imaging Protocols and interpretation and prepares the residents with adequate knowledge on the principles and applications of PET imaging which are integrated in the certifying examination of the Philippine Society of Nuclear Medicine and is essential in their practice as future nuclear medicine physicians.

The government has played its role in the promotion of PET education and training in the country. The Philippine Nuclear Research Institute (PNRI) has nominated and sent several physicians to different Regional Training Courses on PET Imaging organized by the International Atomic Energy Agency (IAEA). In addition, foreign organizations such as the Asian Regional Cooperative Council on Nuclear Medicine (ARCCNM) has granted several awards to different nuclear medicine physicians and residents in the Philippines for their participation in different conferences, including the recently concluded World Congress in Nuclear Medicine and Biology (WCNMB) which highlighted PET

imaging and Molecular Nuclear Medicine. Other foreign funded grants on PET Training has also been awarded to several nuclear medicine physicians,

The Philippine Society of Nuclear Medicine has emphasized the education and training of PET Imaging applications will continue to evolve as dictated by the advances in this field to ensure a dynamic learning process for the residents and physicians.

Conclusion: The five years of PET facility existence in the Philippines have provided adequate cooperative learning and training between nuclear medicine residents and physicians in the principles of PET imaging. Professional and government organizations have continued providing collaborative support, opportunities and training in this field which would make the awareness, education and training in PET Imaging acceptable to international standards. With the rapid development in PET technology, more dynamic training and education opportunities are anticipated for the continued development, cooperative learning and awareness in PET imaging.

Designing an university-level module on molecular imaging chemistry

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Why do we need radiopharmacy, radiopharmacy, radiopharmacy training?
In this post-genomic era, molecular imaging has gain tremendous interest not only amongst physicians but also from biologists, chemists, physicists, engineers, statisticians, pharmaceutical companies and even from governments.

There is no doubt that nuclear medicine has been engaged in molecular medicine more than one decade ago. Positron emission tomography (PET) has reawaken interest in long forgetton radiopharmacy. Only major hospitals in the developed countries have invested in the development of dedicated radiopharmacy laboratory and training or recruitment of radiopharmacist. But PET has forced nuclear medicine to create a radiopharmacy unit and adopt radiopharmacy guidelines such as good radiopharmaceutical practice (GRPP) and good manufacturing practice (GMP). It is compounded by the fact that SPECT radiopharmaceutical chemistry has advanced significantly for both diagnostics and therapeutics, which calls for a high level of understanding on radiopharmaceutical chemistry and technical know-how.

These factors eventually lead to introduction of traning program, courses and degree program. The most striking examples will be European Assosciation of Nulcear Medicine (EANM) radiopharmacy courses and a series of IAEA activities on GRPP, GMP and technologist training programs.

Various forms of training or education program can be formulated for various levels, starting from basic radiopharmacy course to PhD program, depending on the following factors;

(1) National interest and policies on bio/medical sector,
(2) Size of the nuclear medicine community in the respcetive country,
(3) Institution interest and policies, and
(4) Existing infrastructure and programs.

Current Radiopharmacy Education in Singapore
In Singapore, all of the major nuclear medicine centers are supervised by radiopharmacists with PhD degree. All of the nuclear medicine technologists in the major centers have got trianing in radiopharmacy both in theory and hands-on practice. Final-year radiology students in Polytechnic have to go through a series of lectures on radiopharmacy and also practicals in hospital radiopharmacy laboratory. But due to the Government's initiatives on biomedical industries and also due to a global trend, interest in bio/medical imaging is rising among scientists and students. There is a need to fulfil this demand by introducing new course or modules at the University level.

Designing an university-level module on molecular imaging chemistry
In National University of Singapore, a graduate student (MSc and PhD) level 5 module on "Medical Imaging" has already been introduced and a new module on "Molecular Imaging Chemistry" will be introduced soon.

A module of this kind should serve as a link between chemistry, molecular imaging and clinical application with emphasis on chemical probe design. And should introduce contemporary topics and emerging concepts in chemistry related to molecular imaging.

A brief introduction on different modalities of molecular imaging and principles of biomedical

imaging should be introduced including principles of medical imaging equipments. How these knowledge will direct the chemical synthesis should be highlighted (lead directed synthesis). There should be a coverage on pharmacology and drug discovery process as imaging probes could be considered as drugs.

Here is an example of an outline for such module;

Introduction

- What is molecular imaging?
- Why molecular imaging?
- What is biomedical imaging?
- Different modalities of molecular imaging
- Different types of molecular imaging
- *In vitro, ex vivo, in vivo* imaging
- Drug discovery process
- Pharmacological basis

Molecular Imaging Chemistry

- general construct of imaging probe (molecular reporter system)
- Bioimaging factors influencing chemical probe synthesis
- Optical imaging probes
- Radioimaging probes
- MR contrast agents
- Probes for other modalities, X ray, ultrasound, etc.

Examples of practical applications.