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Radiopharmaceuticals and Tumor Detection

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Radiopharmaceuticals and Tumor Detection

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TUMOR LOCALIZATION WITH RADIONUCLIDES

A major goal of research in Nuclear Medicine is the development of a "magic bullet" that will permit reliable localization of malignant tumors by a non-invasive technique applicable to mass screening. No such agent exists at this time. However, tumor imaging does play a major role in the spectrum of procedures which are carried out in the Nuclear Medicine laboratory. Delineation of lesions is possible by several methods, some direct and others indirect.

Possible approaches to tumor localization can be listed as follows:

1. penetration of tracers into tissues which normally exclude them (e.g., brain tumor imaging).

2. imaging of defects in the usual distribution of a tracer (liver imaging).

3. use of agents which are metabolized by normal cells of the tissue being studied (radioiodine in functioning thyroid cancer metastases).

4. assessment of vascularity (labeled human serum albumin, "flow" studies of initial passage of a tracer).

5. evaluation of increased metabolism and protein formation (^{75}Se-selenomethionine uptake, ^{32}P-phosphate).

6. increased uptake of a label as response to injury (^{99m}Tc-phosphate complexes in bone).

7. immune-specific uptake (carcino-embryonic antigen).

8. non-specific agents with unknown mechanism (^{67}Ga-citrate, ^{111}In-bleomycin).

In this section we will be concerned with non-specific agents, primarily. Localization of brain tumors, liver and bone imaging, and assessment of blood flow are discussed elsewhere.

Evaluation of the efficacy of a diagnostic agent includes sensitivity (percent true positives) and specificity (percent true negatives). In addition the tumor type should not be in too broad a histological classification to obscure essential differences among subclasses of tumors.

Practical considerations for tumor localizing agents (as for other diagnostic imaging agents) are:

1. tumor-background ratio (clearance from non-target tissues)
2. blood clearance rate (degree of protein binding, etc)
3. localization in normal structures
4. nature of the radionuclide label (radiation dose, detectability, time of imaging).

It is apparent, from review of the literature, that an "ideal" agent is not yet at hand. It is also apparent that considerable difficulties exist in comparing one clinical series with another. The methods of data presentation differ and the clinical material differs among various series of patients. We have attempted to select data that appeared to have been obtained from a substantial series of patients. Data contained in abstracts were not included.

TABLE I

Radioactive Tumor Localizing Agents

Radionuclide	Half Life	Major Radiation (MeV)	Chemical Form
^{32}P	14.28 days	β^- 1.17 (100%)	Phosphate
^{197}Hg	2.71 days	γ 0.077 (18%)	Chloride
		0.191 (2%)	Chlormerodrin
		0.268 (0.15%)	
^{203}Hg	46.90 days	β^- 0.214 (100%)	Chloride
		γ 0.279 (77%)	Chlormerodrin
^{131}Cs	9.70 days	ϵ X-rays 0.029 (100%)	Acetate
^{129}Cs	1.34 days	γ 0.375 (48%)	Chloride, citrate
		0.416 (25%)	
		0.550 (5.5%)	Citrate
^{206}Bi	6.24 days	ϵ Pb X-ray (100%)	Citrate
		0.184 (21%)	
		0.343 (26%)	
		0.516 (46%)	
		0.536 (34%)	
		0.803 (99%)	
		0.880 (72%)	
		1.720 (36%)	
^{169}Yb	31.8 days	γ 0.063 (45%)	Citrate
		0.110 (18%)	
		0.131 (11%)	
		0.177 (22%)	

TABLE 1 (Cont'd)

Radionuclide	Half Life	Major Radiation (MeV)	Chemical Form
		0.177 (22%)	
		0.198 (35%)	
		0.308 (10%)	
^{75}Se	120.4 days	γ 0.066 (1%)	Selenite
		0.093 (3.3%)	Selenomethionine
		0.121 (17%)	
		0.136 (57%)	
		0.265 (60%)	
		0.280 (25%)	
		0.401 (12%)	
^{131}I	8.05 days	β^-0.806 (100%)	NaI, 19-iodo-cholesterol
		γ 0.080 (2.6%)	Analogs of chloroquine
		0.284 (5.4%)	6-iodo MNDP,CEA
		0.364 (82%)	Iodinated human serum albumin
		0.637 (6.8%)	Anti-fibrinogen
		0.723 (1.6%)	Toluidine blue, Iodofluorescein
^{125}I	60.2 days	γ 0.035 (7%)	Chloroquine analog
^{123}I	13.3 hours	γ 0.183 (83%)	Quinoline analog
^{99m}Tc	6.049 hours	γ 0.140 (90%)	Pertechnetate, bleomycin, HEDSPA, tetracycline
^{111}In	2.81 days	γ 0.173 (89%)	Chloride, citrate

TABLE 1 (Cont'd)

Radionuclide	Half Life	Major Radiation (MeV)	Chemical Form
		0.247 (94%)	Bleomycin
^{57}Co	270 days	γ 0.014 (9%)	Bleomycin
		0.122 (87%)	
		0.136 (11.0%)	
		0.692 (0.14%)	
^{67}Cu	2.44 days	β 0.57 (100%)	Citrate
		γ 0.092 (23%)	
		0.184 (40%)	
^{67}Ga	3.24 days	γ 0.093 (40%)	Citrate
		0.184 (24%)	
		0.296 (22%)	
		0.388 (7%)	

TABLE 2

Radiopharmaceutical	Activity Administered	Use	Comments
^{131}I-NaI	0.5 - 1.0 mCi	Functional carcinoma of thyroid	Post-thyroid ablation
^{123}I	1.0 mCi		
^{111}In chloride	2.5 mCi	General	
^{111}In citrate			
^{111}In bleomycin	1.75 mCi		
^{57}Co bleomycin	0.75 mCi	Pulmonary, primary and metastatic lymphomas, breast, melanoma, head and neck, ovary, brain	
^{99m}Tc bleomycin	3-5 mCi	General	
^{67}Cu citrate	1.0 mCi	Pulmonary, non-specific	
$^{99m}TcO_4$	10 - 20.0 mCi	Breast, non-specific	
^{99m}Tc diphosphonate or polyphosphate	15 mCi	Breast	
^{99m}Tc tetracycline	10 mCi	General	
^{99m}Tc HEDSPA	15 - 20 mCi	Breast	
^{197}Hg Cl	1.5 mCi	Brain	Can't differentiate between benign, malignant or inflammation

TABLE 2 (Cont'd)

Radiopharmaceutical	Activity Administered	Use	Comments
^{203}HgCl	10 µCi/kg	Pulmonary	
^{197}Hg chlormerodrin		Kidney, brain, lung	
^{131}Cs Acetate	0.345 - 2.2 mCi	G.I. and G.U.	
^{129}Cs Chloride	< 4 mCi	Pulmonary, thyroid	
^{169}Yb Citrate	0.1 - 1.0 mCi	General	High radiation dose
^{206}Bi Citrate	0.10 mCi	Breast	Not suitable due to high energy & high radiation dose
^{75}Se Selenite	300 µCi	General	Limited use because of long half-life
^{75}Se Selenomethionine	3.4 µCi/kg (250 µCi usual)	General	
^{131}I-19-Iodocholesterol	2.0 mCi	Adrenal	High radiation dose
^{131}I-Chloroquin analogs		Melanoma	
^{131}I-Toludine blue		Insulinoma	
^{131}I-Iodo MNDP	195 - 490 µCi	General	
^{131}I-Diiodofluorescein	600 µCi	Brain	
^{131}I-Human serum albumin	1.0 mCi	General	
^{67}Ga Citrate	1.0 - 3.5 mCi	General	

TABLE 3

Radiation Dose from the Activity Administered (rad/mCi)

Radiopharmaceutical	Target Organ	Whole Body
^{67}Ga citrate (1)	Kidney 0.51-0.6	0.27
	Colon 1.0	
	Liver 0.5-0.6	
	Spleen 0.5-0.6	
	Gonads 0.19	
^{57}Co bleomycin (2)	Kidney 0.067	0.053
	Gonads 0.067	
^{169}Yb citrate (3)	Bone 11.5	3.48
^{206}Bi (4,5)	Kidney 1.84-48.3	
	Gonads 70-75	1.18
^{131}Cs (6)	Bone 0.15	0.2-0.4
	Gonads 0.2	
	Kidney 0.25	
	Liver 0.2	
^{197}Hg-chlormerodrin (7)	Renal	
	Cortex 12	0.1
	Liver 1.5	
	Ovaries 0.04	
^{203}Hg-chlormerodrin (7)	Renal	
	Cortex 100	1-2
	Liver 19	
	Ovaries 0.77	
^{75}Se L-selenomethionine (8)	Pancreas 12	8
	Kidney 21-23	
	Spleen 16	
	Thyroid 6	
	Testes 11	
^{75}Se selenite (9)	Liver 33	6.4
	Kidney 38	
$^{99m}TcO_4$ (10)	Gonads 0.012-0.016	0.013
	Stomach 0.1	
	Thyroid 0.27	

TABLE 3 (Cont'd)

Radiopharmaceutical	Target Organ		Whole Body
^{99m}Tc bleomycin (11)	Kidney	0.02	.0004
	Bladder	0.02	
^{129}Cs chloride (6)	Bone	.1	.25
	Kidney	0.5	
	Liver	0.4	
	Spleen	0.4	
	Gonads	0.3	
^{111}In chloride (6)	Marrow	2.4	0.5
	Liver	4.5	
	Gonads	0.5	
^{111}In bleomycin (12)	Liver	1.03	0.26
	Marrow	0.94	
^{99m}Tc polyphosphate (13)	Bone	0.06-0.99	0.016-0.24
	Bladder	0.203-3.04	
	Ovaries	0.028-0.42	
^{131}I albumin (6)	Blood	10-15	1-2
	Liver	1-2	
	Gonads	2-5	
^{131}I-NaI (14)	Thyroid	260-1300	0.24-0.71
	Liver	0.2-0.48	
	Stomach	1.7-1.4	
	Ovaries	0.14	
^{131}I-19-iodocholesterol (15)	Adrenals	30.0	0.94
	Testes	2.01	
	Ovaries	2.88	

TABLE 4

Comparison of Scanning with ^{67}Ga-citrate and ^{197}Hg-compounds (16)

Disease	no. positive ^{197}Hg	no. positive ^{67}Ga
Malignant melanoma	20/30 (66%)	36/54 (66%)
Hodgkin's Disease	2/2 (100%)	83/101 (82%)
Non-Hodgkin's lymphoma	6/9 (66%)	38/55 (69%)
Carcinoma bronchus	163/203 (80%)	276/308 (89%)
Mesothelioma	2/5 (40%)	3/5 (60%)
Carcinoid tumor	0/4 (0%)	0/4 (0%)
Pulmonary tuberculosis	36/81 (44%)	19/62 (30%)
Sarcoidosis	3/4 (75%)	32/36 (89%)

TABLE 5

Diagnosis of Breast Masses (17,18)

Radiopharmaceutical	Normal	Positive Findings: Carcinoma	Fibroadenoma	Fibrocystic Disease
^{99m}Tc-polyphosphate and diphosphonate	0/9	9/10	0/1	0/2
^{99m}Tc-pertechnetate	-	4/4	0/1	0/1

TABLE 6

^{99m}Tc-tetracycline for
Tumor Localization (19)

Intracranial	2/3
Chest	11/13
Axilla	2/2
Neck	0/1
Abdomen	1/5
Groin	0/1
TOTAL	16/25 (64%)

In tables 7 through 17 the data has been adapted from a review article (21) which has summarized the literature concerning tumor imaging, with special emphasis on ^{67}Ga-citrate. For specific sources of the data which has been combined in these tables the original review article should be consulted.

TABLE 7

Sensitivity of ^{67}Ga for Detecting Lung Cancer

Type	no. of patients	% positive
All lung cancer	489	93
Squamous carcinoma	93	93
Bronchoalveolar adeno-carcinoma	58	95
Small cell, oat cell	34	88
Large cell, undifferentiated, anaplastic	87	90

TABLE 8

Lung Cancer: Sensitivity of ^{67}Ga Scans in Detecting Surgically Proved Regions of Disease

Anatomic Region	% positive
Lung	90
Regional nodes	73
Bone	71
Brain and other sites	57

TABLE 9

Sensitivity of ^{67}Ga for Detecting Adenocarcinoma

Organ	Patients (no.)	Sensitivity (%)
Lung	58	95
Breast	128	67
Gastrointestinal	78	38
Prostate	11	55
Thyroid	49	27
Pancreas	14	14
Ovary	9	36

TABLE 10

Sensitivity of ^{67}Ga for Detecting Squamous Carcinoma

Region	Patients (no.)	Sensitivity (%)
Lung	93	93
Esophagus	17	41
Cervix	11	36
Head-neck	89	58

TABLE 11

Sensitivity of ^{67}Ga in Detecting
All Forms of Lymphoma

Type	Patients (no.)	Sensitivity
Hodgkin's disease	439	87
Lymphoma, histiocytic predominant	127	75
Lymphoma, mixed cell	20	85
Lymphoma, lymphocytic, poorly differentiated	85	70
Lymphoma, lymphocytic, well differentiated	21	60
"Giant follicular" lymphoma	6	33
Undifferentiated, Burkitt type lymphoma	3	100

TABLE 12

Hodgkin's Disease and ^{67}Ga,
by Histologic Type

Type	%
Nodular sclerosis	75
Lymphocytic predominant	75
Mixed cell	59
Lymphocytic depletion	40

TABLE 13

Sensitivity of ^{67}Ga for Lymphoma
by Anatomic Regions Proved by Surgery

Region	Hodgkin's Lymphoma (%)	Non-Hodgkin's Lymphoma (%)
Neck-axilla	79	50
Thorax	93	78
Abdomen, pelvis	59	53
Inguinal, femoral	50	58

TABLE 14

Non-Hodgkin's Lymphoma:
Sensitivity of ^{67}Ga by Histologic Type

Type	%
Histiocytic (reticulum cell sarcoma)	76
Mixed cell	51
Lymphocytic, well differentiated (lymphosarcoma)	46
Lymphocytic, poorly differentiated (lymphosarcoma)	34
Undifferentiated, pleomorphic	67
Undifferentiated, Burkitts Type	100

TABLE 15

Sensitivity of ^{67}Ga for Marrow Neoplasia

Disease	Patients (no.)	Sensitivity %
Ewing's Tumor	16	100
Leukemia, acute lymphocytic	17	57
Leukemia, acute myelogenous	28	59
Leukemia, chronic lymphocytic	1	0
Leukemia, chronic myelogenous	1	100
Myeloma	12	17

TABLE 16

Sensitivity of ^{67}Ga for Brain Tumors

Tumor	Patients (no.)	Sensitivity %
Metastatic cancer	11	85
Primary brain tumor	28	90
Meningioma	5	80
Glioma, Grade I	1	0
Glioma, Grade II	4	75
Glioma, Grade III	2	100
Glioma, Grade IV	7	100

TABLE 17

^{67}Ga Uptake in Various Malignancies

Tumor	Patients (no.)	Sensitivity %
Thyroid carcinoma	49	27
Anaplastic	9	56
Medullary	3	0
Papillary	7	0
Follicular	1	0
Papillary-follicular	1	100
Melanoma	32	47
Testicular carcinoma	34	57
Seminoma	2	50
Embryonal cell	6	83
Teratocarcinoma	6	33
Renal carcinoma	31	74
Wilms' tumor	4	50
Neuroblastoma	1	100
Basal cell carcinoma	2	0
Uterine carcinoma	1	100
Vaginal carcinoma	2	100

TABLE 18

Comparative Sensitivity of ^{57}Co-bleomycin and ^{67}Ga-citrate for Localizing Tumors (21)

Tumor Type	^{57}Co-bleomycin no. positive	^{67}Ga-citrate no. positive
Epidermoid carcinoma		
Lung	12/13 (92%)	10/13 (77%)
Head and neck	8/8 (100%)	3/7 (43%)
Metastatic	1/2 (50%)	1/2 (50%)
Total epidermoid ca.	21/23 (91%)	14/21 (66%)
Adenocarcinoma		
Breast	1/2 (50%)	0/1 (0%)
Lung	2/2 (100%)	1/1 (100%)
Metastatic	8/10 (80%)	4/8 (50%)
Total adenocarcinoma	11/14 (78%)	5/10 (50%)
Undifferentiated lung carcinoma	5/5 (100%)	4/4 (100%)
Melanoma	2/3 (67%)	1/3 (33%)
Miscellaneous	2/5 (40%)	1/5 (20%)
All malignant tumors	41/50 (82%)	25/43 (58%)

TABLE 19

^{169}Yb-citrate for Tumor Diagnosis (22,23)

	Squamous Cell Carcinoma	Adeno Carcinoma	Undifferentiated Carcinoma	Malignant Lymphoma	Other	Percent Positive
Head and neck	6/7	1/4	1/2	3/4	0	78.5
Chest						
lung (primary)	20/24	4/4	4/6	0	0	75.5
lung (secondary)	3/4	3/3	0	0	1/1	87.5
mediastinum	2/3	1/1	0	0	1/2	66.7
Abdomen	3/7	13/29	0	0/2	11/22	48.3
Pelvis	3/3	1/1	0	0	1/1	100
Extremeties	1/1	3/3	0	0	1/1	100
Total	77.5%	55.3%	62.5%	50%	55.5%	65.9%

Combined series, several hospitals - 235/360 (65.3%)

Lung - malignant tumors - 12/15 (80%)
benign tumors - 0/7

TABLE 20

Efficacy of $^{129}CaCl$ in

Pulmonary Tumor Localization (24)

Type	no. positive
Adenocarcinoma	3/3 (100%)
Squamous cell carcinoma	6/7 (85%)
Undifferentiated carcinoma	6/6 (100%)
Oat cell carcinoma	0/1 (0%)
Total	15/17 (88%)

TABLE 21

Comparison of Sensitivity of ^{99m}Tc-bleomycin and ^{67}Ga-citrate According to Cell Type (11)

Lesions	^{99m}Tc-bleomycin	^{67}Ga-citrate
Primary		
Undifferentiated cell carcinoma	9/11 (82%)	11/11 (100%)
Squamous cell carcinoma	20/25 (80%)	11/18 (61%)
Adenocarcinoma	26/33 (79%)	13/28 (45%)
Malignant lymphoma	3/7 (43%)	7/7 (100%)
Fibro-and myosarcoma	3/3 (100%)	3/3 (100%)
Malignant melanoma	1/1 (100%)	0/1 (0%)
Retinoblastoma	1/1 (100%)	0/1 (0%)
Teratoma	1/1 (100%)	1/1 (100%)
Total	64/82 (78%)	46/70 (66%)
Metastatic		
Undifferentiated cell carcinoma	1/1	-
Squamous cell carcinoma	7/7	2/4
Adenocarcinoma	13/15	5/10
Total	21/23 (91%)	7/14 (50%)

TABLE 22

Comparison of ^{99m}Tc-bleomycin and ^{67}Ga-citrate for Tumor Localization (11)

Region		^{99m}Tc-bleomycin		^{67}Ga-citrate	
Face	Orbital	3/3	11/13 (85%)	0/3	4/9 (44%)
	Paranasal, mouth, mandibular	8/10		4/6	
Neck	Epipharynx and larynx	3/5	11/13 (85%)	5/5	6/10 (60%)
	Thyroid	8/8		1/5	
Chest	Lung	20/22	28/32 (88%)	16/20	19/28 (68%)
	Breast	5/5		1/4	
	Esophagus	3/5		2/4	
Abdomen	Liver and pancreas	6/9	14/18 (78%)	7/9	10/18 (56%)
	Gastrointestinal	8/9		3/9	
Pelvic organ		0/2	(0%)	0/2	(0%)
Extremity cancer and sarcoma		7/8	(88%)	4/6	(67%)
Malignant lymphoma		3/7	(43%)	7/7	(100%)
Total		74/93	(80%)	50/80	(63%)

TABLE 23

Sensitivity of ^{111}In-transferrin for Tumor Localization (25)

Head and neck tumors	7/10 (70%)

TABLE 24

^{75}Se-Selenomethionine as a Tumor Imaging Agent (26)

Sarcomas	no. positive
Rhabdomyosarcoma	6/6 (100%)
Reticulum cell sarcoma	3/3 (100%)
Osteogenic sarcoma	1/1 (100%)
Pleural mesothelioma	3/3 (100%)
Total	13/13 (100%)
Malignant lymphomas	
Hodgkin's disease*	67/69 (97.1%)
Lymphosarcoma	14/14 (100%)
Chronic myelogenous leukemia	2/2 (100%)
Chronic lymphocytic leukemia	2/2 (100%)
Acute lymphocytic leukemia	1/1 (100%)
Total	86/88 (97.7%)
Cancers of Other Origin	
Bronchogenic carcinoma*	7/12 (58.3%)
Breast*	2/15 (13.3%)
Ovary	1/1 (100%)
Prostate*	1/4 (25%)
Malignant melanoma	3/3 (100%)
Malignant hepatoma	0/1 (0%)
Unknown origin	2/3 (66.7%)
Miscellaneous	2/4 (50%)
Total	18/43 (41.9%)

*There was ± localization as follows: Hodgkin's disease (1), bronchogenic carcinoma (2), breast (7) and prostate (1).

TABLE 25

^{75}Se-Sodium Selenite as a Tumor Imaging Agent (27)

Region	no. positive	
Brain		
Primary	31/33	(94%)
Metastatic	12/17	(71%)
Benign	2/13	(67%)
Bone		
Primary	2/3	(33%)
Metastatic	12/26	(46%)
Intrathoracic	15/23	(65%)
Intraabdominal	16/32	(50%)
Head and neck	17/20	(85%)
Cutaneous, subcutaneous	4/5	(80%)
Axillary lymph nodes	5/7	(71%)
Breast	20/30	(67%)

TABLE 26

Efficacy of Various Radionuclides in Brain Tumor Imaging (27)*

Radionuclide	no. positive
^{203}Hg	90/100 (90%)
	54/69 (78%)
$^{99m}TcO_4^-$	75/92 (81.5%)
	134/150 (89%)
	48/50 (96%)
^{131}I-HSA	17/27 (63%)
^{206}Bi	49/56 (87.5%)
^{75}Se	43/50 (86%)

*See original article for individual references.

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