

**Phase III Trial of Adjuvant Radiotherapy vs. Adjuvant Radiotherapy  
plus Systemic Chemotherapy for Local and Regional Neuroendocrine  
(Merkel Cell) Carcinoma of the Skin**

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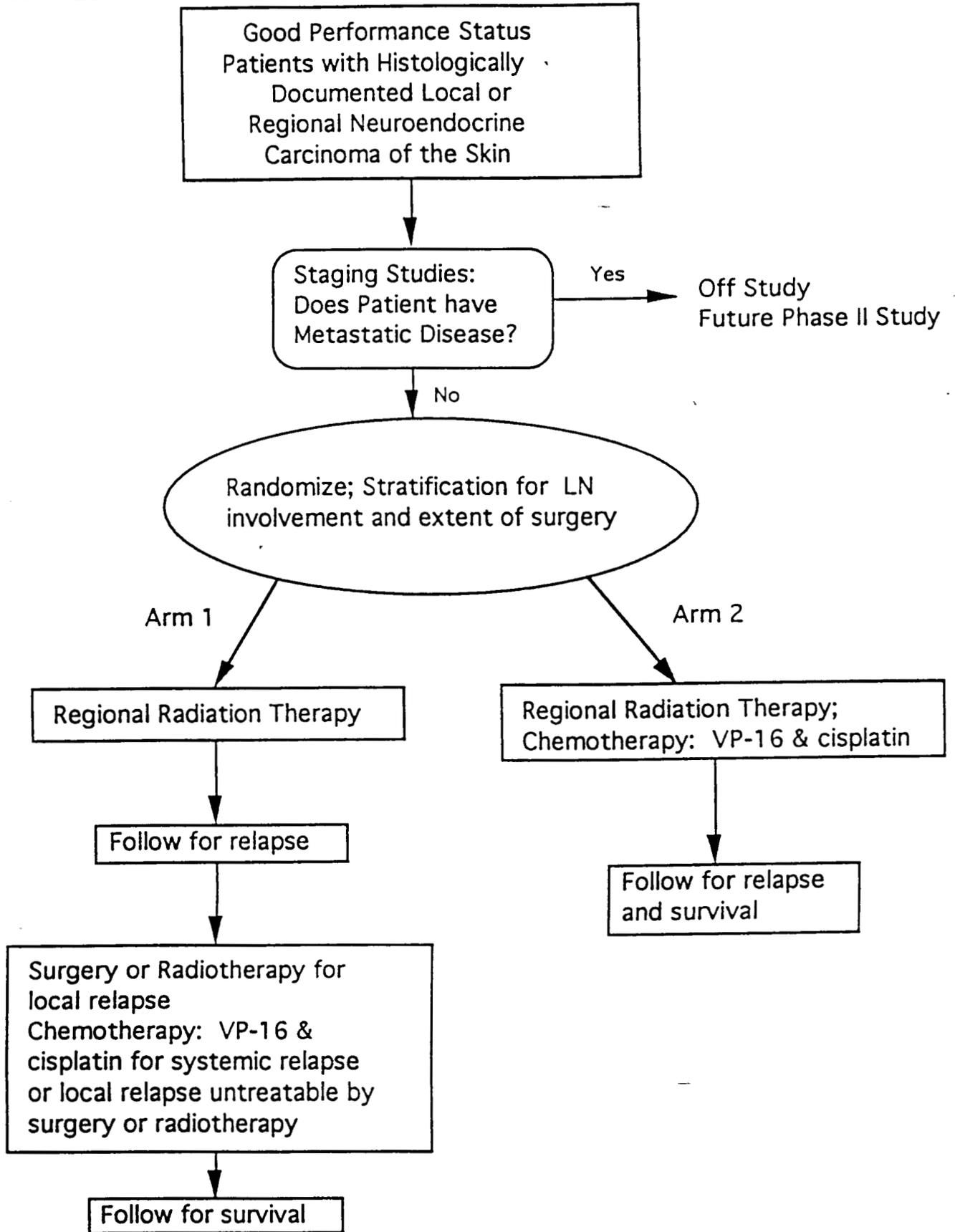
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SCHEMA



## 1.0 PRECIS

Patients with local and regional neuroendocrine (Merkel Cell) carcinoma of the skin (NECS) will undergo metastatic survey. Those with systemic metastasis will be off study while those without metastases will be randomly assigned to postsurgical adjuvant treatment with regional radiation or combined regional radiation and six cycles of systemic chemotherapy with cisplatin and etoposide.

## 2.0 INTRODUCTION

### 2.1 HISTORY AND NOMENCLATURE

In 1972, Toker described 5 cases of a previously unrecognized neoplasm of the dermis which he labeled trabecular carcinoma of the skin (1). Later, in 1978, it was suggested on the basis of ultrastructural studies that the cell of origin of this entity was the Merkel cell (2), an infrequent and scattered tactile cell in the basal layer of the epidermis (3) first described by Merkel in 1875 (4). However, competing theories favor origination from a cutaneous stem cell or from epithelial tumors which develop neuroendocrine differentiation during oncogenesis (5). Thus, of the numerous terms which have been used to refer to the clinicopathologic entity originally described by Toker (Table 1), neuroendocrine carcinoma of the skin (NECS) is most descriptive, does not presume a cell of origin, and will be used in this text.

It should be emphasized that no prospective study on any aspect of NECS has been performed. Thus, the statements in this proposal, which are based on the English language literature on NECS, are based on a synthesis of case reports and retrospective analyses of small series of patients.

### 2.2 EPIDEMIOLOGY

There are over 400 cases of NECS reported in the literature, most in the form of single case reports and small series. The largest single institution series of NECS described 70 patients over a period of twenty years; sixty-six of these were in the last 10 years (6). Chuang calculated the incidence of NECS to be 0.2 per 100,000 (7). However, this was based on one case among the 58,000 residents of Rochester, Minnesota between 1970 and 1984 (7), a time during which NECS was undescribed or not widely recognized. The National Cancer Institute-SEER database, which covers 9.6% of the U.S. population, recorded 68 cases of Merkel cell carcinoma and one case of neuroendocrine carcinoma of the skin in 1987 and 1988. This extrapolates to 300-400 cases per year in the United States. The

actual number of cases may be higher than the number estimated from the SEER database due to misdiagnosis or the use of alternative designations for this tumor.

NECS is primarily found in the elderly with peak incidence in the seventh and eighth decades of life and a mean age at diagnosis of 68 years (range, 7 to 92 years) in reported cases. Approximately three fourths of reported patients are 60 years or older. NECS cases are approximately equally distributed between males and females. Sun exposure is a likely risk factor based on the near exclusive occurrence on sun-exposed body surfaces and an association with other skin tumors found in sun damaged skin (8). In addition, in those instances where race is recorded, NECS is found almost exclusively in Caucasians. Skin complexion has not been reported frequently enough to evaluate this possible risk factor.

Several factors may lead to an a higher incidence of NECS in the future. First, the U.S. population continues to age and NECS is found more commonly among the elderly. Second, increases in the age specific incidence of other skin cancers associated with sun exposure may be an indicator of a greater amount of keratinic damage occurring in persons of all ages. Third, the level of awareness of NECS continues to increase on the part of clinicians and pathologists.

### 2.3 PATHOLOGY

Routine histologic examination of NECS reveals a nonorganoid tumor arising in the dermis composed of uniform small round cells with sparse cytoplasm and round or oval nuclei with small nucleoli. The presence of various neuroendocrine markers detected by immunohistochemistry studies (Table 2) have been used to distinguish NECS from lymphoma, invasive carcinoma, and other small round cell tumors (9). Cytokeratins, neuron-specific enolase, and neurofilament proteins are found most frequently. This pattern of immunohistochemical findings suggests an epithelial origin with neuroendocrine differentiation (5). NECS characteristically stain with cytokeratin and neurofilaments in a perinuclear inclusion-like pattern (10) which is not characteristic of small cell lung carcinoma (SCLC). Ultrastructural studies with electron microscopy show dense core neurosecretory granules similar to SCLC and consistent with a neuroendocrine origin of the tumor. In addition, characteristic perinuclear filament whorls and occasional desmosomes are present (3, 11).

There have been several earlier reports of misdiagnosis based on routine histologic examination that were later found to be NECS by immunohistochemistry or ultrastructural studies (3, 12)

### 2.4 CLINICAL COURSE

NECS typically presents in an elderly Caucasian person as an asymptomatic pink or purple nodule on sun-exposed skin. The site of primary skin involvement is most frequently the head and neck (about 50%) followed by the extremities (about 35%) (13). The mean duration of symptoms (palpable nodule) is 4 months with greater than 90% being present less than one year. The average size of the primary is 2 to 3 cm. Excisional biopsy will frequently lead to the correct diagnosis. Reports of earlier cases of misdiagnosis are less frequent due to a greater awareness of NECS by both clinicians and pathologists. Differentiation of NECS from other skin tumors, lymphoma, and metastatic carcinoma is readily accomplished by immunohistochemical or ultrastructural studies. However, NECS and SCLC overlap in their pathologic findings and to distinguish between these two carcinomas with neuroendocrine differentiation frequently requires consideration of the clinical setting (14).

Approximately two-thirds of patients have disease limited to the primary site at the time of presentation. Primary treatment of localized NECS (see below) varies greatly. Clinically uninvolved regional lymph nodes can be involved with tumor (15). However, the frequency of histologically positive, clinically negative lymph nodes is unknown. Local recurrence of NECS following local treatment of NECS is common (26%) (6) but, in retrospective analyses, does not appear to adversely affect survival (6).

Patients presenting with clinically involved regional lymph nodes constitute approximately 30% of NECS and almost always have tumor involvement of the lymph nodes histologically (15). The occurrence of lymph node metastases appears to be an adverse predictor of survival (6). However, lymph node involvement is not correlated with tumor site, size, or surgical margin. Furthermore, there are no known pathologic features of local or regional NECS which predict the subsequent biologic behavior of this clinically variable tumor. Several cases (3) of spontaneous regression of NECS metastatic to lymph nodes have been described (16-18); one followed shortly after chemotherapy that resulted in no response during treatment.

Less than 5% of patients present with metastatic disease from what is thought to be NECS (13). Common sites of metastasis are lymph nodes, skin, lung, liver, and brain. Less commonly reported sites are pancreas, pleura, bone, kidney, ovary, chest wall, and stomach. Regional lymph node involvement occurs at some point in the course of NECS in at least 50% of patients (6, 13). Distant metastatic disease has been documented in at least 34% of cases (13).

In one series of 70 patients, the predicted actuarial 5-year survival was 64% (6) of whom 19 (27%) died of NECS. However, the median follow-up was only 28 months.

Although no formal staging classification has been adopted by the AJCC, patients are generally classified as having localized (Stage I), regional (Stage II), or systemic metastatic (Stage III) involvement (6).

## 2.5 TREATMENT

2.5.1 Surgery. Nearly all patients reported in the literature have undergone excisional or incisional biopsy of the primary tumor for diagnostic purposes. There is a high local recurrence rate after surgical excision alone [43% in one series (19)]. This has led some authors to recommend wide surgical margins. The effect of the size of the surgical margin on recurrence (local, regional, or systemic) and survival has not been studied prospectively, but wide margins did not appear to decrease local recurrence in one of the larger series (6).

Because of the purported orderly progression of clinically apparent involvement of NECS from primary site to regional lymph nodes to distant metastatic sites several authors have recommended prophylactic regional lymphadenectomy (6). However, the effect of regional lymphadenectomy on recurrence or survival is unknown.

2.5.2 Radiotherapy. The technique of radiotherapy for the treatment of NECS varies greatly due to the limited experience with this tumor, widely scattered sites of tumor, and varying intents (therapeutic vs. prophylactic) of therapy. However, NECS does appear to be radiosensitive. Pacella reported a 96% complete response rate in 23 measurable lesions in 15 patients (20). These lesions included recurrent primary, regional lymph nodes and distant metastatic sites. There was only one in-field relapse. The addition of radiation therapy to surgical excision did not appear to alter the development of metastatic disease (7/19 pts = 37%) or survival (63% actuarial at 2 years) (20).

The optimal strategy for the management of local-regional NECS has not been determined. With respect to local control, surgical excision alone appears inadequate while locoregional radiotherapy, either with or without surgery, appear to result in excellent local control. However, no local treatment scheme has been shown to prevent the development of distant metastatic disease or prolong survival.

2.5.3 Chemotherapy. Experience with chemotherapy in the treatment of NECS is limited with to 70 patients described in the English literature in sufficient detail to be useful. The majority of recent reports use combinations of chemotherapeutic agents which cause high response rates in patients with small-cell lung carcinoma (Table 3). The largest experience with chemotherapy in NECS is in patients with metastatic disease. Combinations containing cyclophosphamide and doxorubicin (Adriamycin) or cisplatin have

caused objective responses in of 77% and 53% of reported cases, respectively (Table 3). Response duration has been only several months (range, 1 to 24 months) with rapid regrowth of tumor typically resulting in the patient's demise.

Experience with chemotherapy in the treatment of locally recurrent tumor or metastases to regional lymph nodes is even more limited (Table 3). Similar combinations containing cyclophosphamide and doxorubicin (Adriamycin) or cisplatin have resulted in a higher percent of responses than in the treatment of metastatic NECS (Table 3). There have been several long term survivors (> 4 years disease free). However, the number of cases is too small and the natural history of NECS too variable to be able to determine from these reports if chemotherapy in this setting improves survival.

Some authors have suggested the use of chemotherapy in the adjuvant setting and a few case reports exist (21-23). However, the routine use of chemotherapy in this setting is not established.

## 2.6 BIOLOGICAL QUESTIONS

Many patients with NECS have tumor that can be easily resected under local anesthesia with low morbidity. Access to such tumor tissue would allow further study of the biology of this unusual tumor. First, if further tumor cell lines are established, more extensive *in vitro* drug sensitivity data could be obtained which might be more generalizable. In addition, comparison of the pattern of abnormalities in the p53 and retinoblastoma tumor suppresser genes between SCLC and NECS may provide further insight into the carcinogenic mechanism of tobacco smoke and UV light, respectively.

## 2.7 SUMMARY

It is amply apparent that NECS is a more aggressive cancer than was described in reports from the 1970's and early 1980's. NECS commonly is recurrent locally and with distant metastatic disease. Improvements in local modalities have likely improved local control, but without demonstrable improvement in survival. Thus, at least a subset of patients with NECS should be considered to have systemic disease at the time of diagnosis. This clinical characteristic along with similarities of pathologic features and sensitivity to radiotherapy and chemotherapy have led to suggestions that NECS be treated in a similar fashion as SCLC.

Thus it is proposed to perform a study to assess the efficacy of treatment of patients with NECS with immediate chemotherapy and radiotherapy and compare the outcome to treatment with surgical excision and radiotherapy alone. Cisplatin and etoposide (VP-16) are proposed as the chemotherapeutic agents, rather than combinations

including doxorubicin and cyclophosphamide, to allow for combined chemo- and radiotherapy in the immediate chemotherapy arm.

### 3.0 OBJECTIVES

- 3.1 Determine the survival, disease-free survival, and pattern of relapse of local and regional NECS treated with adjuvant regional radiotherapy or postsurgical adjuvant combined regional radiotherapy and systemic chemotherapy following surgical excision.
- 3.2 Assess the toxicity of treatment with adjuvant regional radiotherapy or postsurgical adjuvant combined regional radiotherapy and systemic cisplatin and etoposide following surgical excision in patients with local and regional NECS.
- 3.3 Determine prognostic factors for survival, disease-free survival, and sites of relapse in patients with local and regional NECS treated with postsurgical adjuvant regional radiotherapy or adjuvant combined regional radiotherapy and systemic chemotherapy following surgical excision.
- 3.4 Determine the utility of staging studies in patients with local and regional NECS.
- 3.5 Determine the frequency and type of genetic alterations found in local and regional NECS.

### 4.0 PATIENT SELECTION

- 4.1 Histologic diagnosis of NECS and histologic material available for review by the study pathologist.
- 4.2 Clinical Stage I or II NECS (see Appendix A for staging to be used in this study) based on history, physical exam and laboratory (CBC and chemistries) studies. Patients may be enrolled if they have undergone any number or extent of surgical procedures (even if there is no evaluable tumor remaining). Patients may be enrolled no later than 8 weeks after the last surgical procedure.
- 4.3 Efforts should be made to enroll patients prior to the performance of studies listed under metastatic survey (Section 5.7). Patients who have had any study listed under metastatic survey may be enrolled. All studies of the metastatic survey must be performed within 4 weeks of enrollment.
- 4.4 Age  $\geq$  18 years.
- 4.5 ECOG Performance status of 0-2.
- 4.6 Ability to give informed consent, willingness to accept randomly assigned treatment, and a reasonable expectation that the patient will comply with the protocol.

excised. Pathologic staging of clinically uninvolved regional lymph nodes is not required. Clinically involved regional lymph nodes are to be excised if feasible (see Section 7.1)

5.7.3 Metastasis (M) criteria: The following metastatic survey is to be performed after enrollment into the protocol and prior to the initiation of treatment:

- 5.7.3.1 CT scan of the chest with contrast.
- 5.7.3.2 CT scan of the abdomen with contrast.
- 5.7.3.3 CT scan of the pelvis with contrast (only for lesions of the trunk, perineum, or lower extremities).
- 5.7.3.4 CT scan of the brain with contrast.
- 5.7.3.5 Whole body radionucleotide bone scan
- 5.7.3.6 Bilateral bone marrow aspiration and biopsy for patients with clinical evidence of bone marrow involvement or elevation of the LDH only.

CT scans are preferred to MRI scans. However, if already performed, MRI scan of the chest, abdomen, pelvis or brain may be used to fulfill the criteria for the corresponding CT scan.

If one or more of the above listed metastatic survey studies has been performed in the time period between the patient's initial presentation with NECS and consideration of this study, the patient may still be enrolled. In this instance, notation should be made of the indication for performing the test (i.e., to investigate abnormal symptoms, signs or laboratory findings, or to screen for metastatic disease).

Abnormalities detected by the above metastatic survey that suggest the presence of metastatic tumor will be investigated appropriately. If the metastatic NECS is histologically proven, then the patient is off study and should be considered for another study, if eligible.

For each of the above 6 metastatic survey studies (items 5.7.3.1 to 5.7.3.6), analysis of its utility will be performed after 50 patients have received prospective staging with that test. If no more than 6% (i.e., 3 patients) have been found to have metastatic disease by a given test, then subsequent patients enrolled into the protocol will no longer be required to undergo that test.

5.7.4 Final TNM Stage. The above T, N, and M criteria will be used in conjunction with the staging system listed in Appendix A to assign a final stage to each patient.

## 6.0 RANDOMIZATION AND STRATIFICATION

Patient with no evidence of metastatic disease (i.e., a final stage of I or II), will be randomly assigned to treatment with either regional radiotherapy (Arm 1) or combined regional radiotherapy and systemic cis-platinum and etoposide chemotherapy (Arm 2). Patients will be stratified according to stage (Stage I or Stage II) and extent of surgery (with or without regional lymphadenectomy).

All patients will be registered by the research nurse with Orkand Corporation at (301) 402-1732 between 0830 and 1700, Monday through Friday. After registration, the Orkand personnel will determine the patient's treatment group by referral to the randomization and stratification schema.

## 7.0 TREATMENT PLAN

7.1 Surgical Excision. It is anticipated that surgical excision will frequently have been performed prior to consideration of participation in this protocol. All patients must have, at a minimum, surgical excision of clinically evident tumor, at both primary and regional lymphatic sites, if this is technically and physiologically possible. The type and extent (i.e., surgical margin) of each procedure will be recorded. Fresh excised tumor tissue that is not required by the pathologist for clinical purposes should be snap frozen in liquid nitrogen or dry ice and transported on dry ice to the NCI Navy Medical Oncology Branch.

### 7.2 Radiation Therapy.

7.2.1. Equipment. Modality: In general electron beam therapy using the appropriate energy electrons to cover the tumor volume as described in section 8.2.4 will be used to treat the primary tumor/tumor bed. Based on primary tumor location and the extent of tumor megavoltage photon irradiation (Cobalt 60 or linear accelerator with minimum beam energy of 4 MV and maximum energy of 20 MV) may be used to treat the primary tumor/tumor bed. Regional lymphatics, when treated, may be treated with electrons or with megavoltage photon therapy as determined by the treating radiation oncologist.

7.2.2. Radiotherapy Delivery. Technique: If electron irradiation is used, enface beams using custom shaped fields will be used. If photon irradiation is used, single or multiple isocentric fields will be used as determined by the treating radiation oncologist.

### 7.2.3. Timing of Radiotherapy

7.2.3.1 Radiotherapy will commence no later than 8 weeks after surgery. On the chemotherapy arm radiotherapy will commence concurrently with day 1 of the first cycle of chemotherapy.

7.2.3.2 Radiotherapy will be delivered in a continuous course fashion unless breaks are required for toxicity.

### 7.2.4. Volume

7.2.4.1 The primary volume of treatment should include the known extent of tumor at time of diagnosis prior to surgery with a margin. A lateral margin of 5 cm should be used except in cases where a smaller margin is needed to prevent normal tissue toxicity. The deep margin should extend to such a depth as to include the maximum tumor extension (as determined by the biopsy specimen or appropriate radiographic studies) plus 1.5 cm.

7.2.4.2 Uninvolved regional lymphatics will in general be treated prophylactically when such treatment can be accomplished without significant morbidity. In the head and neck region the regional lymphatics will be treated as defined in section 7.2.4.2.1. In other sites (extremities, trunk) the uninvolved regional lymph nodes will be treated if the primary is in close proximity to the regional lymphatics (within 15 cm) and can be treated in continuity or using matching field techniques. For distal lower and distal upper extremity (below knee or elbow) no attempt will be made to treat clinically uninvolved regional lymphatics.

#### Definition of regional lymphatics.

7.2.4.2.1 Head and Neck: In general the ipsilateral first echelon lymph nodes will be treated in all head & neck cases. The specific nodal groups treated will be dependent upon the location of the primary tumor. In order to insure that consistent treatment portals are used at various institutions the following specific guidelines

defining regional lymphatics will be used. Any exception will be discussed with the protocol coordinator prior to the start of treatment. For the purpose of determining the regional nodes in head and neck tumors the area will be divided into regions as noted in Figure 1. Reference lines will include a vertical line extending from the external auditory canal to the vertex of the scalp, (line "A", Fig. 1), a line running parallel to the zygomatic arch, (line "B", Fig. 1) and a vertical line through the ipsilateral commissure of the lip (line "C", Fig. 1).

7.2.4.2.1.1 For lesions of the lips anterior to the commissure (line "C", Fig. 1) the submental, ipsilateral submandibular and jugular digastric nodes will be consider the regional lymphatics.

7.2.4.2.1.2 For lesions of the cheek below the zygomatic arch (line "B", Fig. 1), posterior to the lip commissure and anterior to the external auditory canal the ipsilateral submandibular, jugular digastric and upper anterior cervical nodes superior to the thyroid notch will be considered the regional lymphatics.

7.2.4.2.1.3 For lesions of the forehead and anterior scalp which lie 2 cm anterior to the vertical line through the external auditory canal (line "A", Fig. 1) the ipsilateral preauricular, parotid and jugular digastric nodes will be consider the regional lymphatics.

7.2.4.2.1.4 For lesions of the scalp above the zygomatic arch (line "B", Fig. 1) and within 2 cm of the vertical line through external auditory canal (line "A", Fig. 1) the ipsilateral preauricular, parotid and posterior auricular nodes will be considered the regional lymphatics.

7.2.4.2.1.5 For lesions of the scalp 2 cm posterior to the vertical line through the external auditory canal (line "A", Fig. 1) the ipsilateral occipital, posterior auricular and posterior cervical nodes superior to the thyroid notch will be considered the regional lymphatics.

7.2.4.2.1.6 For lesions of the ear the ipsilateral preauricular, posterior auricular, and jugular digastric nodes will be consider the regional lymphatics.

7.2.4.2.1.7 For lesions of the neck the ipsilateral jugular digastric, anterior and posterior cervical and supraclavicer nodes will be considered the regional lymphatics.

7.2.4.2.2 Proximal Upper Extremities: axillary nodes will constitute the regional lymphatics.

7.2.4.2.3 Proximal Lower Extremities: femoral/inguinal nodes will constitute the regional lymphatics.

7.2.4.2.4 Anterior Thorax/Abdomen: For lesions above an imaginary transaxial plane passing through the umbilicus, the ipsilateral axillary nodes will constitute the regional lymphatics. For lesions below the umbilicus except for the perineum the ipsilateral inguinal nodes will constitute the regional lymphatics. For lesions of the perineum the ipsilateral inguinal and femoral nodes will constitute the regional lymphatics.

7.2.4.2.5 Posterior Thorax/Abdomen: For lesions above an imaginary transaxial plane passing through the umbilicus, the ipsilateral axillary nodes will constitute the regional lymphatics. For lesions below this plane, except for the perineum, the inguinal nodes will constitute the regional lymphatics.

7.2.4.3 Clinically involved regional lymphatics will be treated by lymph node excision, if technically and physiologically possible, and will receive postoperative radiation therapy using doses described in section 7.2.5. Patients who have undergone more extensive resections or who have clinically involved regional lymphatics that are technically or physiologically not resectable are eligible and will receive radiation therapy using doses described in section 7.2.5.

## 7.2.5. Dose

7.2.5.1 Absorbed dose will be defined as cGy to water.

7.2.5.2 Daily dose. The daily dose per fraction will be 200 cGy. Patient will be treated daily, 5 days per week.

7.2.5.3 Dose homogeneity. An attempt will be made to minimize the dose variation within the stated treatment volume and limit such dose variation to no greater than 10 % over the treatment volume.

7.2.5.4 Total dose will be 5000 cGy to the tumor bed with negative surgical margins.

7.2.5.5 Total dose will be 5000 cGy to clinical uninvolved regional nodes or resected regional nodes with negative margins.