

## CLINICAL APPROACH TO NEUROENDOCRINE CARCINOMA OF THE SKIN (MERKEL CELL CARCINOMA)

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### Introduction

Merkel cell carcinoma (MCC) is an aggressive yet uncommon neoplasm that often arises on the head and neck in elderly patients. Toker<sup>1</sup> first described it in 1972 as a trabecular carcinoma of the skin based on its histological characteristics. Based on immunocytochemical and ultrastructural characterization, a variety of other names have been proposed for the neoplasm, including apudoma, neuroendocrine carcinoma of the skin (NEC), primary small-cell carcinoma of the skin, primary undifferentiated carcinoma of the skin, endocrine carcinoma of the skin, anaplastic carcinoma of the skin, and trabecular cell carcinoma. Currently, the terms NEC and MCC are the most prevalently used designations.<sup>2</sup>

Histological differentiation of NEC from other tumors such as undifferentiated small-cell neoplasms or anaplastic metastatic carcinomas is difficult.<sup>1</sup> Ancillary techniques, including electron microscopy and immunohistochemistry, have allowed the dermatopathologist to more accurately differentiate this tumor from other malignancies.<sup>3</sup> Although a relatively rare tumor, NEC has been recognized and reported more frequently in recent years. It has also proven to be an aggressive neoplasm, with overall survival rates of 58% to 79%.<sup>4,5</sup> Because of the rari-

ty of the tumor, however, diagnosis and treatment have previously been based more on anecdotal data than on scientific data. We present an algorithm for the diagnosis and treatment of NEC, recommend multidisciplinary guidelines for this biologically aggressive cutaneous malignancy, and present our experience using this algorithm with 47 patients, 18 of whom underwent selective lymphadenectomy.

### Literature Review

The Merkel cell typically appears as a large, oval, clear cell located in or near the basal layer of the epidermis. It is often confused with melanocytes and Langerhans cells.<sup>5,6</sup> Although the exact function of Merkel cells remains unknown, it is thought that they function as cutaneous mechanoreceptors.<sup>7-11</sup> They are found closely associated with terminal axons<sup>6</sup> and, although found in hairy skin, glabrous skin, and mucous membranes, they are concentrated in the skin of acral areas.<sup>6,12</sup> They are usually found in clusters associated with nerve endings forming specialized, slowly adapting mechanoreceptors such as the tactile hair disk, the hederiform ending of Merkel-Ranvier found in glabrous skin, nose, lip, palate, and genitalia, and the Merkel touch spots (Tastscheiben) found on the palpebral margin of the eyelid.<sup>6,8,13-15</sup>

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The origin of the Merkel cell remains unconfirmed. Several hypotheses have been suggested, including the neural crest,<sup>6,7,16,17</sup> epidermal origin as a modified keratinocyte,<sup>9,18-20</sup> and the amine precursor uptake and decarboxylation (APUD) system.<sup>17,21-23</sup> Indeed, the Merkel cell exhibits immunocytochemical properties of both epithelial and neuroendocrine cells. They share desmosomes with adjacent keratinocytes and display paranuclear staining with low-molecular-weight cytokeratins.<sup>18</sup> Neuroendocrine markers displayed by Merkel cells include neuron-specific enolase, chromogranin A, and synaptophysin.<sup>19,20</sup>

Just as there is controversy concerning the origin of the Merkel cell, the histogenesis of NEC remains yet to be fully elucidated. Tang and Toker,<sup>24</sup> using ultrastructural analysis, suggested that the neoplasm arises from neural crest-derived cells, most likely the Merkel cell. Subsequent studies have supported the origination of NEC from the Merkel cells, in which both are shown to contain bundles of intermediate filaments and cytoplasmic secretory granules.<sup>21,23,25-28</sup> Likewise, the majority of NECs react with antibodies to low-molecular-weight cytokeratins similar to those expressed by normal Merkel cells,<sup>27-30</sup> and immunohistochemical studies show both NEC and Merkel cells expressing neuroendocrine markers such as enolase,<sup>31</sup> chromogranin A,<sup>19</sup> and synaptophysin.<sup>20</sup> Despite the ultrastructural and immunohistochemical similarities, however, many

authors do not accept the concept that NEC derives from Merkel cells. They cite the evidence that NEC arises in the dermis and Merkel cells are found in the epidermis, a site rarely involved by NEC.<sup>29,30,32</sup> In addition, NEC infrequently expresses vasoactive intestinal peptide and met-enkephalin, two important markers of normal Merkel cells.<sup>30</sup> An alternative hypothesis of tumor origination is that NEC arises from an immature, totipotential stem cell that acquires neuroendocrine features during malignant transformation.<sup>30,33-35</sup> Therefore, we prefer the term "neuroendocrine carcinoma of the skin" to Merkel cell carcinoma.

NEC is a disease of the elderly, mainly occurring in persons 65 years of age or older, although a range of ages 7 to 97 has been reported.<sup>3,36-39</sup> The mean age in our study was 71.7 years. NEC usually presents as a painless, red to violet nodule on sun exposed areas of skin, similar in appearance to basal cell carcinoma.<sup>5,38,40</sup> The most frequently involved sites for primary lesions include the skin of the head and neck (50% or more), followed by the extremities (40%) and trunk (10% or less).<sup>36,39,44</sup> NEC occurs almost exclusively in whites, although there have been documented cases in blacks and Polynesians.<sup>39,41,45,46</sup> Most recent studies have cited an equal incidence in men and women.<sup>3,38,39</sup> NEC has been reported in persons presenting concurrently with squamous cell carcinoma, basal cell carcinoma, Bowen's disease, and actinic keratoses.<sup>34,41,46-49</sup> The

predilection for sun-exposed skin in elderly whites and in conjunction with other malignancies known to be associated with ultraviolet light exposure has implicated prolonged sun exposure as a possible etiological factor.<sup>3,50</sup> The presence of primary lesions presenting on non-sun-exposed areas such as the buccal mucosa, genitalia, and posterior auricular regions indicates other etiological factors are also important.<sup>50-52</sup>

NEC is a high-grade, aggressive cutaneous malignancy with a propensity for local recurrence and regional lymph node metastasis, similar to malignant melanoma. Local recurrence develops in 26% to 44% of patients after excision of the primary tumor<sup>3,10,34,38,39</sup> and is usually apparent within 4 months.<sup>16</sup> Local recurrence as a predictor of survival is controversial. Two comprehensive statistical analyses failed to show a correlation between the two,<sup>3,5</sup> although this was not found to be the case in a review by Shaw and Rumball.<sup>39</sup>

Regional lymph node involvement occurs in 55% to 66% of patients<sup>50,53</sup> and is apparent at initial presentation in 12% to 31%.<sup>3,5,38</sup> The median time between treatment of the primary tumor and clinically detectable nodal metastasis is 7 to 8 months.<sup>3,5,50</sup> In patients with nodal involvement, 11% to 66% die of their disease within 5 years.<sup>10,38,39,54</sup>

Systemic disease is associated with a particularly poor prognosis. Although rare at initial presentation, one third of patients will develop distant metastases, with

the most commonly involved sites being liver, bone, brain, lung, and skin.<sup>38</sup> Nearly 50% of patients followed for 24 months will develop systemic metastases with a mortality rate of 67% to 74%.<sup>38</sup>

The clinical behavior and pattern of metastases are similar between NEC and malignant melanoma. Lymph node involvement frequently occurs before systemic disease with either NEC or malignant melanoma, and an orderly progression or cascade of metastases has been proposed.<sup>4,36,39</sup> An important prognostic factor in malignant melanoma is the finding of metastases in regional lymph nodes.<sup>55</sup> Although there is no conclusive evidence that this is true for NEC, the survival rate for patients with NEC and lymph node metastases or systemic disease parallels that of malignant melanoma.<sup>5,39,50</sup>

Because of the high degree of local recurrence and early lymph node and distant metastases in patients with NEC, patients should be treated aggressively at the time of initial diagnoses. Although no widely adopted classification system exists, treatment guidelines have been based on three clinical stages of disease: local disease without lymph

node or systemic involvement (stage I), regional lymph node development without systemic disease (stage II), and systemic metastases (stage III).<sup>5</sup> Most treatment guidelines include wide excision of

the primary tumor, alone<sup>3,42</sup> or in combination with adjuvant radiation therapy,<sup>3,5,56-58</sup> therapeutic regional lymph node dissection,<sup>3,39,50</sup> or elective regional lymph node dissection.<sup>42,50</sup>

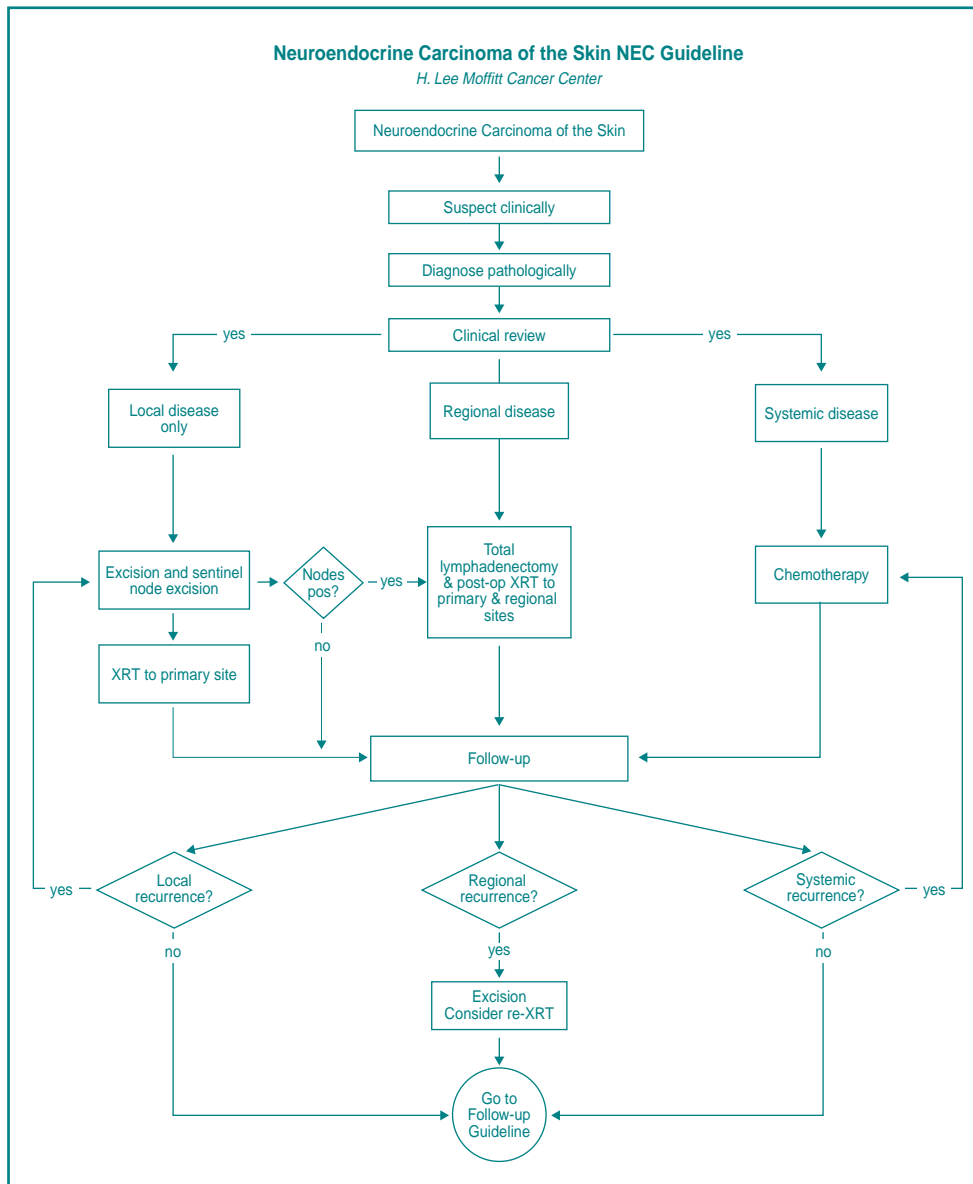


Fig 1. — Based on the findings that NEC shows an orderly progression of spread, this treatment guideline has been developed at our center for patients with NEC by identifying those patients who would benefit from further regional surgery and/or radiotherapy at the time of treatment of the primary tumor.

Although no studies have conclusively demonstrated the efficacy of these treatments in improving long-term survival, an increased time to recurrence<sup>57</sup> and decreased incidence of local recurrence and locoregional failure after locoregional irradiation or elective lymph node dissection<sup>42,54</sup> have been demonstrated.

Based on the findings that NEC shows an orderly progression of spread, we attempted to establish treatment guidelines for patients with NEC by identifying those patients who would benefit from further regional surgery and/or radiotherapy at the time of treatment of the primary tumor (Fig 1). We used a technique recently introduced for melanoma patients — selective lymphadenectomy — to

identify lymph node basins at risk for metastases. It has been shown that the histopathology of the sentinel node reflects the histology of the remaining nodes in the basin.<sup>59,60</sup> We propose that this technique and the guidelines set forth may lead to more effective treatment of patients with newly diagnosed NEC by identifying patients who may benefit from regional nodal dissection and possible adjunctive radiotherapy.

## NEC Guideline Annotations

### *Suspect Clinically*

Neuroendocrine carcinoma of the skin usually presents as a rapidly growing, firm, nontender, solitary

dermal nodule on sun-exposed areas of skin with a slightly red to violaceous color.<sup>5,38</sup> The overlying skin is usually intact, smooth, and shiny, although ulceration may be present.<sup>5</sup> Occasionally, telangiectases may be found overlying the tumor, mimicking basal cell carcinoma. The differential diagnosis includes basal cell carcinoma, adnexal tumor, lymphoma, adult neuroblastoma, melanoma, and metastatic small cell carcinoma.<sup>4</sup> Regional metastasis presents as enlarged, firm, regional lymph nodes. Systemic disease may present as masses in the skin, lung, liver, bone, brain, and other solid organs.<sup>38</sup> The site of distant metastases does not necessarily correlate with the location of primary tumors.<sup>3</sup>

### *Diagnose Pathologically*

The diagnosis of NEC is confirmed by examination of hematoxylin-eosin (H&E)-stained sections and a panel of immunohistochemical stains including high- and low-molecular-weight cytokeratins, S-100 protein, leukocyte common antigen (LCA), and neuron-specific enolase, according to accepted guidelines.<sup>61</sup> The tumors should demonstrate the characteristic trabecular or sheet-like dermal proliferation of monomorphic cells with frequent mitoses and apoptotic bodies (Fig 2).<sup>36</sup> NEC is difficult to diagnose by conventional light microscopy alone<sup>50</sup> due to its histologic similarity to other poorly dif-

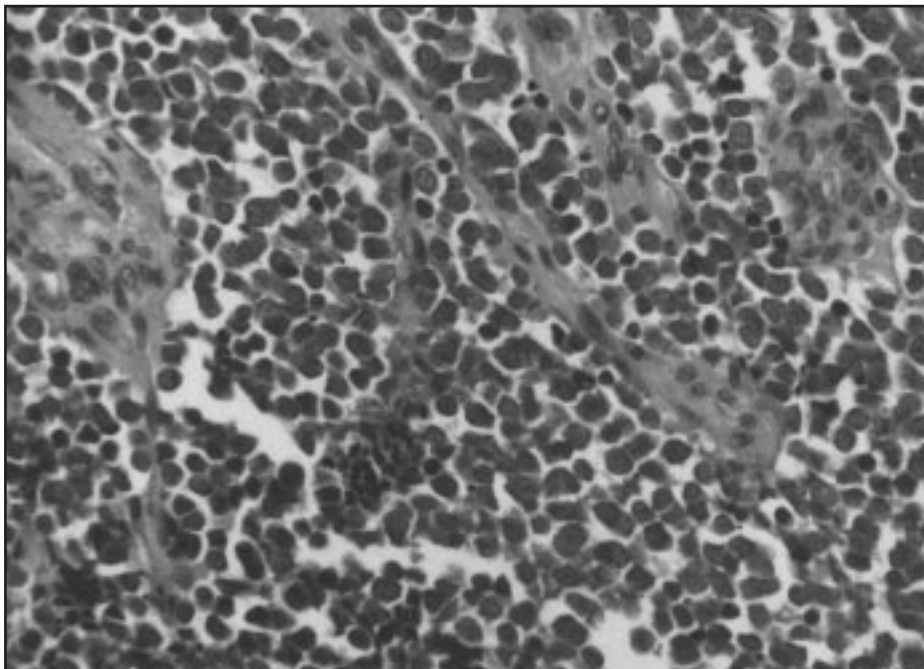


Fig 2. — Merkel cell carcinoma, skin biopsy, demonstrating cords and sheets of medium-sized monomorphic cells with hyperchromatic nuclei and minimal cytoplasm (hematoxylin-eosin,  $\times 400$ ).

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ferentiated neoplasms including metastatic small cell carcinoma of the lung, cutaneous large cell lymphomas, neuroblastoma, metastatic carcinoid, amelanotic melanoma, sweat gland carcinoma, medullary carcinoma, histiocytosis X, and Ewing's sarcoma.<sup>25,26,41,62,63</sup> Definitive diagnosis of NEC is made by demonstrating positive reactivity with antibodies to low-molecular-weight cytokeratin (often in a perinuclear dot pattern) and neuron-specific enolase and negative reactivity for S-100 protein, LCA, and high-molecular-weight cytokeratin.<sup>36,61</sup>

### *Clinical Case Review*

All cases of NEC of skin are presented at the Weekly Multidisciplinary Conference of the Cutaneous Oncology Program with a review of patient history, physical examination, pathological data, radiologic studies, and laboratory evaluation. Recommended baseline data include pathological tissue review, chest radiograph, complete blood cell count, liver function test, and alkaline phosphatase level. Based on this information, the case is classified as either clinical stage I (local disease only), clinical stage II (regional disease), or clinical stage III (systemic disease).

### *Local Disease*

Clinical stage I disease is found in the skin only, with no evidence of regional or systemic disease.<sup>5</sup> It appears as a dermal nodule, as described above, unless an excisional biopsy has previously been done. A larger nodule may be found fol-

lowing incisional biopsy, and ulceration may be present. It is important to determine the extent of local disease, adherence to underlying structures, and proximity to surrounding anatomical structures.

### *Excision of Primary Tumor and Sentinel Node Biopsy*

Excision should include the primary tumor with a 2-cm margin of surrounding normal appearing skin.<sup>4,38</sup> The margin may be modified to save surrounding structures for aesthetic and functional considerations. Two thirds of patients with local disease have been shown to develop regional nodal metastases.<sup>4</sup> Since there are no useful, reliable factors to determine the relative risk of regional metastases, all patients should be considered at high risk. Nodal failures as high as 60% have been documented when not electively managed, indicating a role for nodal sampling.<sup>57,64</sup> Sentinel lymph node biopsy is a useful technique because there is less inherent morbidity than with total lymphadenectomy. This technique includes preoperative radiolymphoscintigraphy and cutaneous tattooing of the location of the sentinel lymph nodes, intraoperative localization of the sentinel lymph node with vital blue dye Lymphazurin injection, and radiolymphoscintigraphic localization with preoperative radioactive sulfur colloid injection and handheld gamma counter localization as described below.<sup>60</sup>

Lymphoscintigraphy is a valuable radiologic technique in pre-

dicting lymphatic drainage in patients with cutaneous melanoma.<sup>17</sup> Compared with standard anatomical guidelines, lymphoscintigraphy has been shown to be more reliable in identifying lymph node basins at risk for metastasis.<sup>65</sup> It can be used to identify the location of the first ("sentinel") nodes (SLN) of the basin, which are most likely to harbor micrometastasis. Patients are preoperatively injected with 450  $\mu$ Ci of technetium-99 antimony sulfur colloid around the primary site and imaged as described previously.<sup>65</sup> The identified locations of the SLNs are tattooed.

The technique of intraoperative lymphatic mapping using aqueous 1% Lymphazurin blue (U. S. Surgical Corp, Norwalk, Conn) has been described elsewhere.<sup>59,60,66</sup> Immediately preoperatively, 1.0 cc of the dye is injected intradermally around the primary site. After a brief uptake period, the tattooed location of the sentinel node identified by preoperative lymphoscintigraphy is exposed. A 2-cm to 4-cm incision is made over the mark. Afferent lymphatics identified by pale blue staining are followed to the sentinel node, which is also tinged a blue color. The sentinel node is excised and submitted for histologic examination. Complete lymph node dissection is performed under general anesthesia only in patients with positive sentinel node biopsies.

Intraoperative radiolymphoscintigraphy augments intraoperative blue dye lymphatic mapping and involves the intradermal injection of an average of 500  $\mu$ Ci of

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technetium-sulfur colloid around the site of the primary melanoma 2 to 16 hours prior to the harvest.<sup>53</sup> Similar to the vital dye, the radiolabeled tracer is taken up by the lymphatics and tracks a path from the primary to the lymph nodes in the regional lymphatic basin. A hand-held gamma probe is used to identify the sentinel node in the basin by greatest intensity of radioactivity. When convenient, other nonsentinel hot nodes are also harvested in the basin for control purposes. After the nodes are removed, the lymphatic basin is scanned with the hand-held gamma probe for radioactivity. A low level of activity in the basin confirms that the sentinel node has been removed, and the high level of activity in the node can be measured *ex vivo* to further assure complete removal.

Lymph nodes removed at the time of sentinel node biopsy are serially sectioned and completely submitted. Specimens obtained are then stained conventionally with hematoxylin-eosin and immunohistochemically with anti-cytokeratin cocktail (AE1/AE3), using a three-step avidin-biotin-peroxidase complex procedure.

### *Radiotherapy to Primary Site*

Radiotherapy to the primary site is recommended after excision because of high local recurrence rate and the aggressive nature of the tumor.<sup>5,38</sup> Several authors have offered specific indications for the use of radiation therapy after excision and to the

draining lymphatic bed, including tumors greater than 1.5 cm in diameter,<sup>50</sup> histological evidence of angiolymphatic invasion,<sup>50</sup> tumors approximating the surgical margins at resection,<sup>39</sup> and locally unresectable tumors.<sup>5</sup> Dosing schedules for radiation therapy have been variable. Most authors agree that doses of 40 to 60 Gy to the surgical bed and draining regional lymphatics in a standard dose fraction regimen are appropriate.<sup>58,64,67</sup>

### *Regional Disease*

In clinical stage II disease, 7% to 31% of patients present with enlarged nodes (larger than 2 cm) in regional basins.<sup>5,39</sup> Fine-needle aspiration may be used to document regional disease preoperatively. It is important to determine the extent of regional disease and adherence to underlying structures. Patients with positive sentinel nodes have micrometastatic regional disease and are classified with pathological stage II disease; these patients are further treated with complete lymphadenectomy and postoperative radiotherapy to the regional site. There is some evidence for a survival benefit in patients treated with locoregional radiation therapy at the time of diagnosis.<sup>57</sup> There is also evidence of increased time to recurrence<sup>57</sup> and decreased incidence of local recurrence and locoregional failure after locoregional irradiation or elective lymph node dissection.<sup>42,54</sup> If the sentinel node is negative, then the patient is considered clinical stage I and should be followed closely for recurrence.

### *Systemic Disease*

Clinical stage III disease usually presents in the bone, abdomen, skin, mediastinum, lung, liver, or basin.<sup>38,68</sup> The usual time span from diagnosis of stage III disease to death is 8 months. Chemotherapy is the treatment most often employed within this setting. However, as in the case of all other treatment modalities used against this tumor, the rarity of the condition precludes the availability of statistically significant comparisons.<sup>68</sup> No firmly established chemotherapy for MCC exists. Because of the neuroendocrine features of this tumor, it has been treated with etoposide and cisplatin as well as with cisplatin and 5-fluorouracil. More recently, there are anecdotal reports of responses to paclitaxel. Unfortunately, the rarity of this tumor has prevented cooperative efforts to establish a firm basis for a recommended therapy.

### *Follow-up*

Aggressive tumors need frequent follow-up. The patient should return to the treating physician for a history and physical examination every 3 months for a period of 3 years and to his or her physician annually thereafter for appropriate follow-up. The history and physical examination should place special consideration on a total body skin examination and palpation of lymph nodes. Depending on clinical presentation, additional laboratory and/or radiological studies should be obtained at this time to investigate symptoms.

## Local Recurrence

Local recurrence will develop within 1 year in 30% to 40% of patients.<sup>2,4,38,39</sup> Diagnosis should be confirmed with a biopsy of any clinically suspicious nodules at the primary site. If recurrence is present, treatment consists of local excision with at least a 2-cm margin and further radiotherapy if possible. If there is no evidence of regional and systemic disease, then re-treat as for local disease only. Elective radiotherapy to nodal basins may also be applied depending on sentinel node sampling or extent of recurrence. If biopsy is negative for local recurrence, then the patient should continue with regular follow-up as scheduled.

## Regional Recurrence

Most regional recurrence develops within 1 year.<sup>4</sup> There is a 50% recurrence rate within 2 years.<sup>38</sup> Diagnosis should be confirmed with a biopsy of any clinically suspicious nodes at the regional disease site or with fine-needle aspiration of suspicious nodes. If regional recurrence is present, treatment should include further excision of the lymph node basin if possible and consideration for further radiotherapy. If regional recurrence is absent, then the patient should continue with regular follow-up as scheduled.

## Systemic Recurrence

Up to 36% of patients will develop systemic involvement, ranging from 11 days to 96 months

after diagnosis (mean = 18.3 months of follow-up). In patients with more than 24 months of follow-up, 49.3% developed distant metastases.<sup>38</sup> Diagnosis should include histological proof of systemic disease in the presenting solid organ or a very high suspicion of metastasis. Treatment should include chemotherapy with individual considerations and the limitations of chemotherapy in mind. If systemic recurrence is absent, then the patient should continue with regular follow-up as scheduled.

## Results

A computer-assisted query of the pathology patient data base at our institute revealed a total of 47 patients with the diagnosis of NEC from 1986 through 1998. Of these, 7 have developed local recurrence and 9 have developed regional

lymph node metastases for a total of 16 (34%) in the course of their disease. Eighteen of the 47 patients consented to participate in a surgical protocol that consisted of preoperative lymphoscintigraphy, intraoperative mapping, and selective lymphadenectomy. The patient data are presented in Table 1. In the study population, a total of 31 sentinel lymph nodes were obtained from these 18 patients. Five lymph nodes from 4 patients demonstrated metastatic disease (Table 2). One patient with a lower extremity primary had a positive sentinel node from the groin. Subsequent complete nodal dissection demonstrated one of the remaining 15 nodes to have metastasis. This patient received postoperative irradiation and has not had any recurrence with a follow-up time of 18 months. One patient with a dorsal nose primary had bilateral positive cervical sentinel nodes. Subse-

Table 1. — Location of Primary Tumors and Lymph Node Involvement

Location of Primary	Number of Patients (n=47)	Initial Treatment	Lymph Node Involvement
Head & neck	14	WLE	5/14
	6	WLE & regional LN	None
	9	WLE & SLN	2
Upper extremity	2	WLE	None
	1	WLE & regional LN	None
Lower extremity	5	WLE & SLN	1
	2	WLE & regional LN	None
Trunk	3	WLE & SLN	1
	4	WLE	2/4
	1	WLE & SLN	None

LN = lymph node  
SLN = selective lymphadenectomy  
WLE = wide local excision

quent left neck dissection revealed 1 of 31 other nodes with metastatic disease, and right neck dissection contained 45 negative nodes. This patient also received postoperative irradiation and has not had any recurrence with a follow-up time of 39 months. Another patient with a left cheek primary tumor had a positive sentinel node from the left neck. A radical neck dissection was done at the time of the sentinel

node and no further nodes were positive for metastatic disease. This patient has not had a recurrence with a follow-up of 12 months. The final patient had a right arm primary with a positive sentinel node from the right axilla and is awaiting further complete lymph node dissection. Immunohistochemical staining of the positive sentinel nodes with anticytokeratin antibodies revealed rare single cells within

either the subcapsular sinus or the body of the node representing micrometastatic NEC. An example of this is demonstrated in Fig 3. No further surgical therapy was undertaken in the patients with negative sentinel node biopsies. Two patients developed local recurrence when the sentinel node biopsy was negative during a median follow-up time of 22 months (maximum 52 months). Of these 2 patients, 1 has received irradiation and has not had a recurrence at 8 months of follow-up, and the other is awaiting radiotherapy. Locoregional recurrence in the remaining 12 patients has been negative with a median follow-up time of 24.5 months with a range of 6 to 52 months.

There were no complications of either preoperative or intraoperative mapping procedures, including no episodes of hypersensitivity. After the injection of Lymphazurin dye intraoperatively, some of it appeared in the urine within 24 hours.

## Discussion

NEC is a rare, aggressive neoplasm that has been reported with increasing frequency in recent years. The causes of this increase are likely twofold: a statistical relationship to sun exposure<sup>5,38</sup> and increasing recognition by pathologists.<sup>3</sup> NEC is an aggressive cutaneous malignancy with a high rate of recurrence and a propensity for early regional lymph node metastasis. Local recurrence will develop in 26% to 44% of patients after excision of the primary tumor,<sup>3,10,34,38,39</sup>

Table 2. — Sentinel Node Excision\*

Patient	Primary Site	Sentinel Node	Nodes Excised
1	Right lower leg	Right groin	2 sentinel (-), 2 non-sentinel (-)
2	Left chest	Left groin	3 sentinel (-), 2 non-sentinel (-)
3	Right thigh	Right groin	1/2 sentinel (+), 1/15 groin dissection (+)
4	Left wrist	Left axilla	1 sentinel (-)
5	Left forehead	Left preauricular, left cervical	4 sentinel (-), 1 non-sentinel (-)
6	Left forearm	Left axilla	1 sentinel (-)
7	Dorsal nose	Left, right cervical	2/2 sentinel (+), 1/31 left radical neck dissection (+), 45 right radical neck (-)
8	Left 5th digit	Left axilla	2 sentinel (-), 1 non-sentinel (-)
9	Left scalp	Left scalp	1 sentinel (-), 1 non-sentinel (-)
10	Right forearm	Right axilla	1 sentinel (-)
11	Right temple	Right neck, right parotid	2 sentinel (-), 4 non-sentinel (-)
12	Left ear helix	Left postauricular	1 sentinel (-)
13	Lip	Right neck, cervical	1 sentinel (-)
14	Left great toe	Left groin	2 sentinel (-)
15	Left postauricular	Left neck	1 sentinel (-), 5 non-sentinel (-)
16	Left cheek	Left neck	1/3 sentinel (+), radical neck (-)
17	Dorsal nose	Left jugular	1 sentinel (-)
18	Right arm	Right axilla	1 sentinel (+), 13 axillary dissection (-)

\* Data of selected patients with NEC at Moffitt Cancer Center from 1986 through 1998.

and 55% to 66% will develop regional nodal involvement during the course of their disease.<sup>50,53</sup> The pattern of spread of NEC has been likened to malignant melanoma in which an orderly progression of lymphatic metastases has been demonstrated.<sup>5,54</sup> Although overall mortality rates are difficult to interpret due to the rarity of the malignancy and lack of long-term follow-up common in an elderly population, the effects on long-term survival in patients with regional and systemic metastases are similar for both melanoma and NEC.<sup>5,38,50</sup> Unlike melanoma, however, there are no histological or clinical prognostic factors that consistently predict which patients will develop metastases.

Because of the propensity of NEC for local recurrence and early regional metastases, treatment should be early and aggressive. Most authors advocate wide local excision of the primary tumor with 1-cm to 3-cm margins.<sup>4,5,38,69</sup> Although it is accepted that patients with demonstrable nodal disease should undergo regional lymphadenectomy, it is controversial if patients without grossly evident nodal disease should undergo prophylactic regional lymph node dissection.<sup>38,50,52,70</sup> Because of regional metastases rates of greater than 50%, some authors recommend prophylactic nodal dissection at the time of primary tumor excision for all patients, although it is unknown if this prolongs sur-

vival.<sup>5,10,50,70</sup> Others have advocated nodal dissection only for patients with head and neck primaries,<sup>5,50,55</sup> for tumors greater than 1.5 cm,<sup>3</sup> when lymphatic or vascular invasion is histologically evident,<sup>38,41</sup> or for lesions present for at least 6 weeks or of unknown duration.<sup>58</sup>

In the present study, our algorithm took advantage of selective lymphadenectomy, a frequently used surgical technique in patients with malignant melanoma. Because of the proposed orderly lymphatic progression of metastases in both malignant melanoma and NEC, it has been shown that the histopathology of the sentinel node represents the histology of the remaining regional nodes.<sup>59,60</sup>

This technique allows staging of a patient's disease without the morbidity of complete nodal dissection. Of the 47 patients in our study, 18 underwent selective lymphadenectomy. Four of these 18 demonstrated sentinel lymph node positivity and went on to have complete lymph node dissections as well as irradiation of the primary tumor site and regional lymph node basin. Two of these 4 patients demonstrated regional lymph nodes positive for NEC beyond the sentinel node. All 4 of these patients have been negative for locoregional recur-

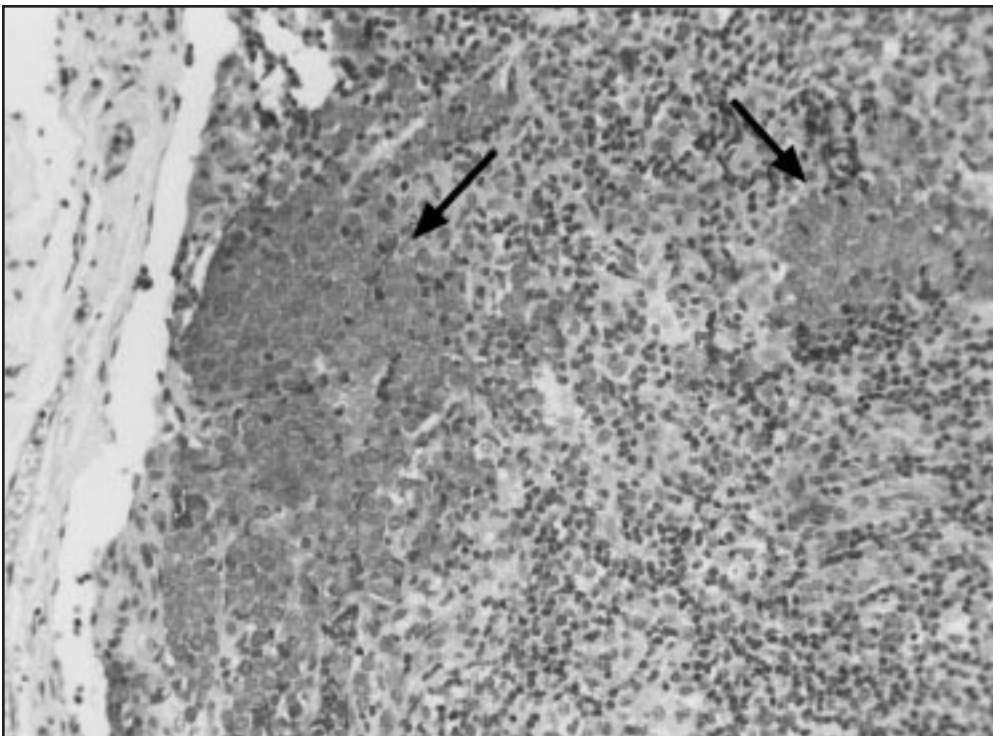


Fig 3. — Sentinel lymph node of patient #7, demonstrating two subcapsular aggregates of metastatic Merkel cell carcinoma (arrows) (hematoxylin-eosin,  $\times 250$ ).

rence in short-term follow-up (longest follow-up of 39 months with a median of 10.5 months).

Selective lymphadenectomy has several advantages in the management of patients with NEC. It facilitates staging of these patients and allows resection of a possible regional lymphatic metastasis before systemic metastasis occurs, yet it spares patients with negative sentinel nodes and no evidence of regional disease the morbidity of a complete nodal dissection. All 12 of the patients in this study who underwent selective lymphadenectomy with negative results have been without disease for a median follow-up of 24.5 months (range = 6 to 52 months). These results parallel that of malignant melanoma in which only 2% of cases with negative sentinel nodes have developed locoregional failure.<sup>59,60,66</sup>

An additional benefit of the lymphoscintigraphy and selective lymphadenectomy regimen is that it identifies the draining lymph node basin with greater accuracy compared with anatomic methods alone. In fact, drainage patterns of patients with melanoma identified by lymphoscintigraphy were discordant in 32% to 63% when compared to relying on anatomic guidelines alone.<sup>65</sup> Therefore, performing complete nodal dissections and irradiation without correctly identifying the sentinel node may result in treatment failures in patients with NEC because the wrong basin was treated. It is important to perform lymphoscintigraphic mapping before

performing wide local excision. Not doing so may result in changes in the lymphatic draining pattern and incorrect identification of the sentinel nodes.

Since NEC is a radiosensitive neoplasm, many authors have advocated its use in the treatment of primary tumors alone and in conjunction with either surgery or chemotherapy. A significant survival benefit has been demonstrated in some studies in patients treated with adjuvant irradiation.

Chemotherapy is the treatment most widely used in patients with systemic disease. NEC appears to respond to various chemotherapy agents initially, but the response is typically short lived.<sup>68,71-73</sup> Because of the rarity of the condition, statistically significant data are not available and no firmly established chemotherapy for NEC exists.<sup>68</sup>

## Conclusions

NEC is a rare neoplasm without definitive treatment guidelines. Based on our experience with this condition, we have attempted to establish treatment guidelines for patients with various stages of NEC. Early results with this algorithm are promising. The combination of selective lymphadenectomy and irradiation has been shown to improve survival rates compared with radiotherapy alone. In addition, selective lymphadenectomy may allow more accurate treatment with less morbidity to the patient. As our

patient data base expands, we will be better able to evaluate the efficacy of this algorithm.

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