Neuroendocrine (Merkel Cell) Carcinoma of the Skin

Its Natural History, Diagnosis, and Treatment

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Over 400 cases of neuroendocrine (Merkel cell) carcinoma of the skin (NCS) have been reported. This tumor continues to pose problems in diagnosis and effective treatment for physicians unfamiliar with its biological characteristics. Reported here are five additional cases of NCS and the literature for this rare neoplasm is comprehensively reviewed. An early and accurate diagnosis is made possible by combining clinical presentation with results of histologic study, immunoperoxidase staining for neuron-specific enolase (NSE), epithelial membrane antigen (EMA), cytokeratins, and electron microscopy. NCS is an aggressive tumor. Depending on the length of follow-up, up to 40% of tumors locally recur, 55% develop regional nodal metastases, and 36% undergo distant metastasis. Survival is sex, but not age, dependent, with an overall 2-year survival rate of 72% (males 58% *vs.* females 79%). No standard procedure for initial and/or follow-up treatment for NCS exists. The authors recommend that NCS be treated, whenever possible, using the same rationale as applied for the treatment of squamous cell carcinoma of the skin.

IN 1972, TOKER COINED THE TERM "trabecular carcinoma" to describe a poorly differentiated carcinoma of the dermis and subcutaneous tissue identified in five elderly people.[1] To date, over 400 cases of this primary cutaneous neoplasm have been reported under a variety of terms[2–65] that include: neuroendocrine carcinoma of skin,[6,8] Merkel cell tumor or carcinoma,[9] primary small-cell carcinoma of the skin,[10] APUDoma,[11] extra-pulmonary carcinoma of the skin,[49] and endocrine carcinoma of the skin.[50] The term neuroendocrine carcinoma of the skin (NCS) is preferable and describes the histologic, ultrastructural, and immunohistochemical features of the tumor without ascribing a cell of origin.

Although the clinicopathologic features of NCS have been widely described, this tumor continues to be a problem for clinicians unfamiliar with its biological characteristics. The natural history of NCS remains to be defined. Currently, these tumors are considered to be aggressive with a variable prognosis.[50] They are difficult to treat effectively and few guidelines for their treatment have been reported.[46,50,55,60,65]

This study was designed to examine the clinical and pathologic differential diagnostic criteria and biological behavior of NCS. Five additional cases of this tumor are described in conjunction with an extensive review of the literature. This review addresses further the clinical presentation, behavior, and response to therapy of this neoplasm.

Methods

Five cases of NCS have been seen at the University of Florida's Shands Teaching Hospital (STH) and the Gainesville VA Medical Center (GVAMC) since 1982. Three were seen as a primary lesion, whereas the remaining two were referred to the Department of Surgery for further treatment. All charts were reviewed and the clinical data verified.

Tissue was fixed in 10% neutral buffered formalin and processed for routine histologic evaluation. Tissue was processed by standard procedures for ultrastructural analysis. Formalin-fixed, 5-μm paraffin sections of tumor and appropriate controls were used for immunoperoxidase staining. The avidin-biotin staining method

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of Hsu[66] was used in conjunction with antibodies to neuron-specific enolase (NSE), epithelial membrane antigen (EMA), cytokeratin (CK), and neurofilaments (NF) for staining of representative sections from each tumor.

Results

Case 1

A 52-year-old white man presented to the GVAMC with a 2-month history of a firm, painful, mass in the axillary tail of the left breast. Currettings were interpreted as consistent with infiltrating ductal carcinoma. One month later, he had a radical left mastectomy for two discrete 2.5-cm tumor nodules and an excisional biopsy of a contralateral, subcutaneous parasternal mass. Histologic and ultrastructural studies were consistent with NCS. In 2 months, regional and distant nodal metastases were observed. Multiple nodal, cerebral, and cutaneous lesions, but no lung lesions, were noted on CT scan at 3 months. He received palliative whole brain radiation therapy (3000 rads) and three courses of chemotherapy consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (50 mg/m^2), and vincristine (2 mg). Initial tumor regression followed, with subcutaneous and cerebral recurrence occurring at 10 months. The patient died with tumor 12 months after his initial presentation.

Case 2

A 70-year-old white man with a 3-year history of well-differentiated lymphoma treated with cyclophosphamide and prednisone presented to STH with a 6-month history of a 3.5-cm firm, cutaneous nodule of the left thigh. The nodule was excised and interpreted as an "undifferentiated malignant neoplasm." Two months later he was diagnosed as having recurrent lymphoma and began a 28-month course of chemotherapy consisting of prednisone (80 mg) and chlorambucil (50 mg). At 17 months he had a 1.5-cm subcutaneous nodule on the left thigh, which was excised and interpreted as being consistent with NCS; wide local excision of the thigh lesion was performed with no residual tumor noted. The patient is currently alive at 36 months with no evidence of disease (NED).

Case 3

A 62-year-old white woman presented to a local physician with a subcutaneous lesion of unknown duration on the left buttock that had been incised and drained. The lesion enlarged and was excised at 4 months, with pathologic characteristics consistent with NCS. At 5 months she was observed to have left inguinal adenopathy, as well as recurrence at the previous excision site. At 6 months she was referred to STH for treatment, and a superficial inguinal node dissection and a wide excision of the original recurrent buttock lesion were completed. NCS was identified in specimens from both sites. She was subsequently treated with radiation therapy to both the inguinal areas (5000 and 6000 rads to the medial and left inguinal regions, respectively) and to the buttock (1000 rads). She is currently alive at 17 months and remains NED.

Case 4

A 67-year-old white man presented to a local physician with an 8-mm subcutaneous nodule of the forehead of 10 months' duration. The findings of an excisional biopsy were interpreted as NCS. Four months later he underwent a superficial right parotidectomy for metastatic tumor. He was subsequently treated at a second hospital with three courses of chemotherapy consisting of cyclophosphamide (750 mg/m^2), CCNU (70 mg/m^2), and methotrexate (15 mg/m^2), with subsequent subjective response. At 9 months he was observed at GVAMC to have an 8.0-cm right neck mass and cervical adenopathy. At 11 months, right parotidectomy and a conservative right neck dissection were completed. Tumor was found in 12 of 20 nodes, in extranodal tissue, and at the margin of resection in several sites. Radiation therapy was given to both the surgical bed (2000 rads) and to the ipsilateral neck (6000 rads). CT-guided biopsies demonstrated abdominal metastatic lesions at 19 months. Chemotherapy consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (45 mg/m^2), and VP-16 (50 mg/m^2) was begun, but the patient was lost to follow-up after one course. He was readmitted to GVAMC at 26 months with a recurrent abdominal mass and restarted on the previous chemotherapy regimen with marked shrinkage in the tumor mass. He is currently alive at 28 months with no clinical evidence of tumor.

Case 5

An 82-year-old white man presented to STH with a 2-cm, rapidly enlarging, subcutaneous gluteal mass of 5 months' duration. The findings of the initial biopsy were interpreted as an "unusual primary carcinoma consistent with Merkel cell carcinoma." The tumor was widely excised at 1 month and diagnosed as NCS. At 8 months, regional adenopathy developed and the patient underwent a right superficial inguinal node dissection. Metastatic tumor was found in 5 of 11 nodes as well as in an extranodal soft tissue. No further treatment was initiated at that time. Eighteen months after presentation, lytic lesions of the T7 vertebrae were apparent, for which he received 3000 rads of local radiation therapy. He is currently alive at 27 months with metastatic disease.

Our five patients had a characteristic presentation of NCS. They were elderly patients, ranging from 52 to 82 years of age, who had a history of a slowly enlarging, firm skin nodule. The tumors ranged from 0.8 cm to 3 cm in maximal dimension, and were located on the lower extremities in three cases, and one each on the chest and the face. Results of the initial histologic interpretation of these lesions demonstrate the necessity of using additional diagnostic techniques. The initial lesion in two cases was misinterpreted; with the correct diagnosis of NCS being made on subsequent review. Contributory is the fact that NCS has a spectrum of histologic appearances that range from lymphomas, invasive carcinoma, and other small round cell tumors. In general, NCS was noted to be a monomorphic, nonorganoid, small round cell tumor arising in the dermis (Fig. 1). Electron microscopic studies demonstrated the presence of electron-dense, neurosecretory type granules in the cytoplasm and cell processes, as well as collections of intermediate filaments and immature cell junctions (Fig. 2). Immunoperoxidase staining for NSE, EMA, and cytokeratins demonstrated both intra- and intertumor variations. NSE was consistently demonstrated, whereas staining of paraffin sections for NF was very inconsistent.

The clinical behavior of NCS in these five patients was consistent with that of a biologically aggressive tumor. Local recurrence was observed in four patients (cases

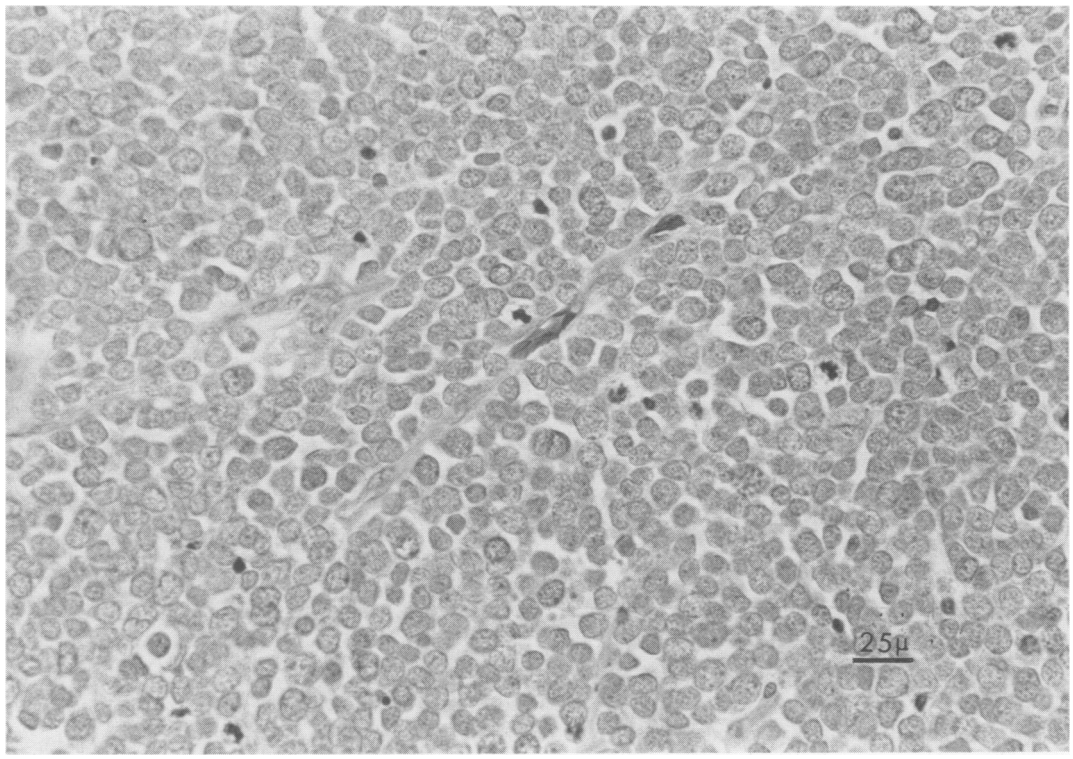

FIG. 1. Pathologic features of neuroendocrine carcinoma of the skin. Hematoxylin and eosin stain of sheets of monomorphic tumor cells (original magnification ×250).

1–4) with an average of 6 months (range: 1–17 months) from the time of presentation. Regional nodal metastases developed in case 5 without prior local recurrence, whereas cases 1, 3 and 4 progressed to regional nodal involvement 1–9 months after diagnosis. Distant metastasis occurred in three of the four patients (cases 1, 4,

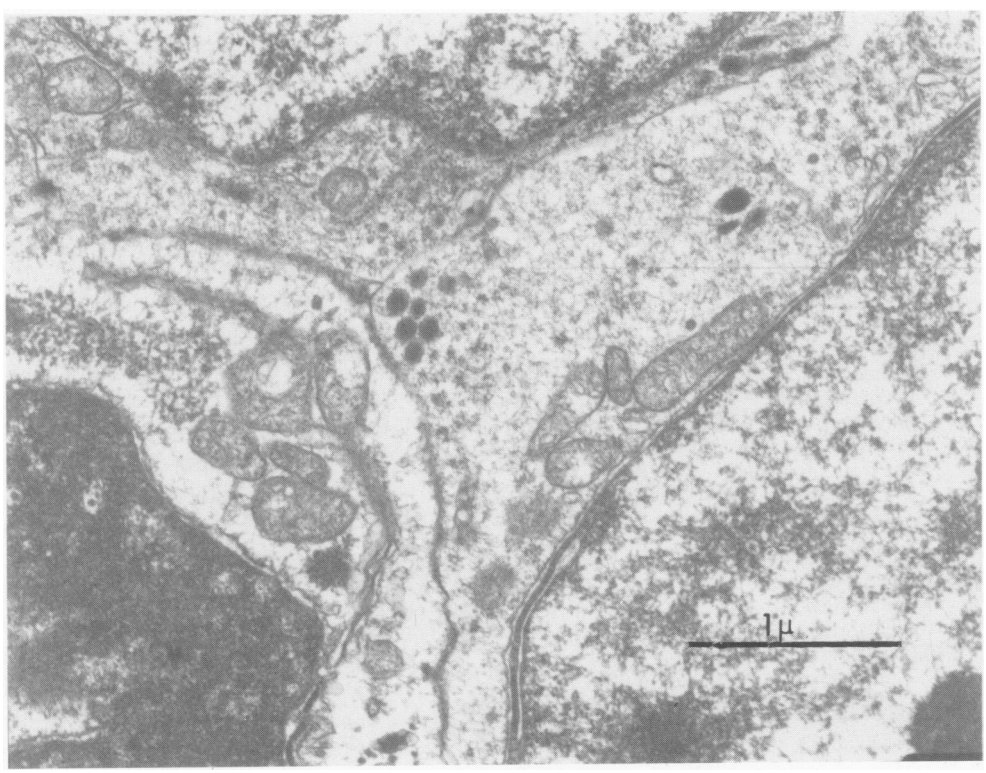

FIG. 2. Ultrastructural features of neuroendocrine carcinoma of the skin (×28,000). Note the presence of neurosecretory-type electron-dense granules and primitive intercellular junctions.

TABLE 1. *Clinical Features of Neuroendocrine Carcinoma of the Skin at Presentation*

Age (years)	
Range (N = 332)	15–97
Mean (N = 269)	68.2
Sex (N = 316)	
Male	48.1%
Female	51.9%
Primary lesion site (N = 315)	
Head and Neck	48.9%
Upper Extremities	15.6%
Lower Extremities	30.2%
Trunk	3.8%
Multiple	1.5%

and 5) with nodal involvement 3–19 months (mean: 13.3 months) after initial presentation. Only case 1 has died of tumor.

Discussion

Neuroendocrine carcinoma of the skin is an infrequent, but by no means rare, primary cutaneous neoplasm. To date, the natural history of NCS remains undefined. The reason for this deficiency is best explained by the fact that previous studies have focused on the pathologic rather than the clinical and/or the biological features of the tumor. The elucidation of these features will aid pathologists and clinicians to initiate both a prompt diagnosis and effective therapy. We have added five additional cases to the over 400 cases of NCS reported in the literature,[1–65] and have undertaken a comprehensive review of the reported cases. Our purpose is to better comprehend NCS's biological behavior, to delineate its essential diagnostic features, and to propose guidelines for its treatment.

TABLE 2. *Clinical Behavior of Neuroendocrine Carcinoma of Skin*

	No. of Patients (%)
Local recurrence	
Patients with ≥6 months F/U*	80/220 (40.0)
Multiple 30/88 (34.1%) (range 2–9×)	
Time from initial diagnosis to first local recurrence: 1–54 months (mean: 10.1 months)	
Regional lymph node metastasis	
All patients	
At presentation	31/254 (12.2)
Following initial diagnosis	86/187 (46.0)
Patients with ≥12 months F/U	107/193 (55.4)
Time from initial diagnosis to nodal metastasis: 1–202 months (mean: 13.4 months)	
Distant metastasis	
All patients	82/226 (36.3)
Multiple sites	10/82 (12.2)
Patients with ≥24 months F/U	73/148 (49.3)
Time from initial diagnosis to distant metastasis: 11 days to 96 months (mean: 18.3 months F/U)	

F/U = follow-up.

NCS is primarily a lesion of sun-exposed skin of the elderly (Table 1). Essentially 50% of reported NCS lesions are located on the head and neck, whereas less than 5% involve the skin of the trunk. Patient age is reported to vary from 15 to 97 years with a mean of 67.9 years. There is no apparent sexual predominance as has been reported previously.[23,25,32,41,50,59,60,65] Patients often have a history of a slowly enlarging, pink to violaceous plaque or nodular subcutaneous lesion that suddenly rapidly increases in size.

NCS behaves as an aggressive tumor with local recurrence and metastases as common features (Table 2). Forty per cent of the patients who were followed a minimum of 6 months or who died before this time, exhibited local recurrence, with close to one third having multiple recurrences. The mean time from diagnosis to first local recurrence was 10.1 months in 220 cases (range: 1–54 months). Approximately 75% (53 of 71) of reviewed cases with local recurrence and 6 months or more follow-up exhibited disease progression with regional nodal and/or distant metastasis. Of these 53 patients, 29 (55%) died of tumor, whereas 30% were alive at the time of publication (Table 3).

NCS has a propensity for early involvement of regional lymphatics (Table 2). Regional nodal metastases were evident in 55% of the reported patients who were followed for 12 months or more, or who died before this time. Adenopathy was noted from 1 to 202 months (mean: 13.4 months) after initial diagnosis. Nodal involvement at the time of initial presentation was observed for 31 of 254 patients (12.2%). A total of 37 of 74 (50%) patients with regional nodal metastasis subsequently developed distant metastases, of which 27 (73%) died of the disease. Only six of 74 (16.2%) reported patients have died of tumor without further metastatic disease developing (Table 3).

Distant metastases occurred in 82 of 226 (36.3%) reported cases of NCS; 10 of 82 (12.2%) exhibited multiple metastases (Table 2). Of the 148 patients with a reported follow-up of 24 months or greater, or who died before this interval, 73 (49.3%) had distant metastatic disease. The mean time from initial diagnosis to discovery of metastatic tumor was 18.3 months (range: 11 days to 96 months). Sites for distant metastatic disease in order of decreasing frequency include: lymphatics, liver, bone (including vertebrae, as in case 5), brain (as in case 1), lung, and skin. Retroperitoneal lymph nodes (as in case 1) are the most common site for distant nodal spread. Involvement of the parotid gland (as in case 4) is consid-

TABLE 3. *Patient Follow-up Status for Local, Regional, and Distant Metastases*

	No. of Patients	Patient Status				
		LTFU	Alive	AWT	DOC	DOD
Local recurrence ≥6 months F/U						
No further lesions	18 (25.3%)	3 (16.6%)	12 (66.7%)	—	2 (11.1%)	1 (5.3%)
Local LN Mets only	19 (26.8%)	3 (15.8%)	8 (42.1%)	—	5 (26.3%)	3 (15.8%)
Local LN/Dist Mets	23 (32.4%)	0	5 (21.7%)	1 (4.3%)	0	17 (73.9%)
Distant Mets only	11 (15.5%)	1 (9.1%)	2 (8.2%)	—	0	8 (72.7%)
Total	71 (100%)	7 (9.9%)	27 (38.0%)	1 (1.4%)	7 (9.9%)	29 (40.8%)
Regional LN metastasis ≥12 months F/U						
No Further Mets	37 (50%)	2 (5.4%)	21 (56.8%)	0	8 (21.6%)	6 (16.2%)
Subsequent Dist Mets	37 (50%)	3 (8.1%)	5 (13.5%)	2 (5.4%)	0	27 (73.0%)
Total	74 (100%)	5 (6.8%)	26 (35.1%)	2 (2.7%)	8 (10.8%)	33 (44.6%)
Distant metastasis ≥24 months F/U						
Literature 1*	64	4 (6.3%)	10 (15.6%)	6 (9.4%)	1 (1.5%)	43 (67.2%)
Literature 2†	77	—	20 (26.0%)	—	—	57 (74.0%)

* Literature 1: excludes patients reported by Silva et al.[50]

† Literature 2: excludes 18 patients reported by Silva et al.[50] and excludes LTFU, and DOC patients and alive includes AWT patients.

LTFU = lost to follow-up; AWT = alive with tumor; DOC = dead from other causes than tumor; DOD = dead of disease; F/U = follow-up; LN = lymph node; Mets = metastasis.

ered to be by direct extension rather than by metastasis.[60]

Death from tumor has been reported to vary from 67% to 74% (Table 3) for patients with distant metastases. For 45 patients in whom precise clinical information was available, death from tumor occurred within an average of 6.2 months from diagnosis of widespread metastatic disease.

The overall prognosis for patients with NCS has been reported to vary. A Kaplan-Meier survival analysis of cases, both those reported and including our five cases, is seen in Figure 3. Overall survival rates are: 1-year, 88%; 2-year, 72%; and approximately 55% at 3 years. The lack of sufficient numbers of patients with 3 or more years of follow-up precludes accurate determination of survival. There was no significant correlation between survival and patient age. Female survival was significantly greater ($p = 0.0069$ Wilcoxon) than that for males. Two-year and 3-year survival rates for males and females were, respectively, 58% *versus* 79.4% and 35.6% *versus* 67.6%.

The metastatic potential of NCS mandates that an early and accurate diagnosis be made by the clinician and the pathologist. The majority of these lesions arise in the dermis and extend into the subcutaneous fat. The spectrum of histology of NCS can make a definitive diagnosis difficult. Goepfert et al.[46] reported that misdiagnosis was as great as 66% when light microscopy was used alone. The differential diagnosis for NCS includes: metastatic oat cell carcinoma, lymphoma, amelanotic melanoma, and adnexal tumors. The correct diagnosis is best derived from a combination of a thorough clinical evaluation, coupled with light and electron microscopy with a defined panel of immunoperoxidase stains. Three principle ultrastructural features aid in differentiating NCS from these other tumors: 75–200-nm electron-dense neurosecretory type granules, paranuclear bundles of intermediate filaments (fibrous bundles),[60] and primitive (nondesmosomal) junctional complexes (Fig. 2). These features are not associated with other primary cutaneous tumors. Immunoperoxidase staining for NSE, EMA, and cytokeratins is highly recommended. Monoclonal antibody to the leukocyte common antigen (LCA) can be used on paraffin sections to rule out a diagnosis of lymphoma.

Treatment guidelines are designed and implemented after thorough clinical evaluation and regular follow-up. The following guidelines for the clinical management of

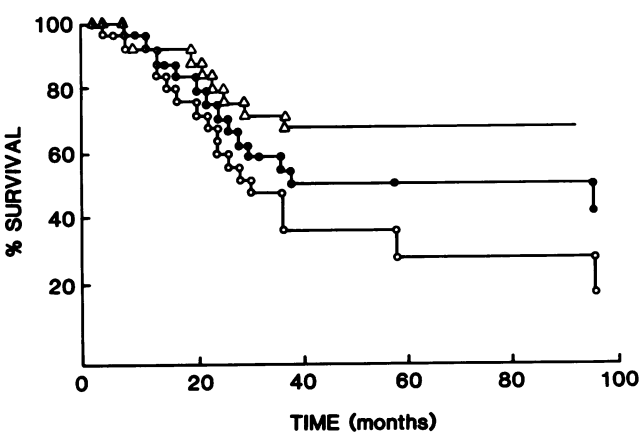

FIG. 3. Kaplan-Meier survival analysis of 172 patients with neuroendocrine carcinoma of the skin. Females have a significantly greater ($p < 0.007$) survival at 24 and 36 months compared with males.

NCS are based on our experiences as well as those of others reported in the literature.

Among reported cases, surgical treatment for primary NCS has varied from incision and drainage to wide excision. Local recurrences arise primarily from an inadequate excision of the primary tumor (the tumor approximates or contaminates the margins of resection). Reported tumors vary from 4 mm to 12 cm, with two thirds being 2 cm or less in greatest dimension. Thus, the majority of the lesions are amenable to excision. We and others[41,46,50,60,65] recommend a wide excision (2–3-cm margin) of the primary lesion be performed with similar techniques implemented for squamous cell carcinoma of the skin.

Prophylactic nodal dissection has not been completed on a routine basis. Silva et al.[50] recommended nodal dissection be performed if the primary tumor was 2 cm or greater, if there is a high mitotic rate (10 HPF), or if the hyperchromatic cell pattern predominates. Relative to head and neck lesions, these authors recommend nodal dissection be performed when the primary tumor is situated in proximity to the nodal regions.[46] We concur that a therapeutic regional nodal dissection be performed for adenopathy as well as for the presence of vascular invasion. In addition, all patients with a primary tumor of the head and neck should undergo radical neck dissection as Goepfert et al.[46] have reported a 75% failure rate for untreated nodes. Patients with midline head and neck primary tumors should undergo bilateral radical neck dissection, which may be staged. Should prophylactic regional node dissection not be initiated, careful patient education and interval physician examination are prudent.

NCS is a radiosensitive tumor.[50,65] Irradiation has been used prophylactically as well as for recurrent and metastatic lesions. Silva and co-workers[46,50] consider that radiation therapy failures are "geographic misses" due to inadequate field margins. They recommend prophylactic radiation therapy be used to reduce local recurrence and/or metastasis. We recommend that radiation therapy be completed in the following cases: (1) where the tumor approximates the margin of resection, (2) when there is histologic evidence of vascular space involvement, and/or (3) if nodal metastasis is present. In these clinical settings, radiation portals should include the tumor bed and the lymphatics in transit. Silva et al.[50] have reported no radiation therapy failures for doses $\geq$ 4500 rads delivered over 5 weeks. Until a dose-response curve is available for NCS, we believe that equivalent irradiation dosage should be administered.

Chemotherapy has been used in the treatment of NCS where there has been an absence of local tumor control. To date, a wide variety of cytotoxic agents have been used and include: VP-16, cisplatin, CCNU, methotrexate, vincristine, doxorubicin, and cyclophosphamide. These regimens have been applied with variable objective response being reported. Kroll and Toker[20] note that tumor regression with chemotherapy was rapid but that recurrence occurred within 6–12 months. Other studies have reported similar results.[50,55,60] The infrequent incidence of the tumor precludes a prospective study for determination of the superior drug regimen. We are currently using cyclophosphamide, doxorubicin, and VP-16 to treat systemic disease in one of our patients (case 4). We and others[50] recommend that the same regimen used for the treatment of oat cell carcinoma should be considered for the treatment of systemic NCS.

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