Sinonasal Malignancies with Neuroendocrine Differentiation

Patterns of Failure According to Histologic Phenotype

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BACKGROUND. Sinonasal neuroendocrine tumors are rare malignancies that are represented by a spectrum of histologies, including esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinoma (NEC), and small cell carcinoma (SmCC). The authors reviewed their institutional experience to determine whether sinonasal neuroendocrine tumors of different histologies have distinct clinical characteristics that warrant individualized treatment approaches.

METHODS. The authors treated 72 adults with pathologically proven, nonmetastatic, primary sinonasal neuroendocrine tumors from 1982 to 2002. There were 31 patients with ENB, 16 patients with SNUC, 18 patients with NEC, and 7 patients with SmCC. Patients with ENB usually were treated with local therapy alone (surgery and/or radiotherapy); only 3 of 31 patients (9.7%) received treatment (radiation) to regional lymphatics, and only 5 of 31 patients (16.1%) received chemotherapy. In contrast, patients with non-ENB histologies usually received chemotherapy (10 of 16 patients with SNUC, 12 of 18 patients with NEC, and 5 of 7 patients with SmCC), and nonsurgical locoregional therapy was used more frequently (6 of 16 patients with SNUC, 4 of 18 patients with NEC, and 5 of 7 patients with SmCC).

RESULTS. The median follow-up for surviving patients was 81.5 months (range, 6–266 months). The Kaplan–Meier estimate of overall survival at 5 years was 93.1% for patients with ENB, 62.5% for patients with SNUC, 64.2% for patients with NEC, and 28.6% for patients with SmCC ($P = 0.0029$; log-rank test). The local control rate at 5 years also was superior for patients who had ENB (96.2%) compared with patients who had SNUC (78.6%), NEC (72.6%), or SmCC (66.7%) ($P = 0.04$). The regional failure (RF) rate at 5 years was 8.7% for patients with ENB, 15.6% for patients with SNUC, 12.9% for patients with NEC, and 44.4% for patients with SmCC. Additional late events increased the RF rate for patients with ENB to 31.9% at 10 years. The distant metastasis rate at 5 years was 0.0% for patients with ENB, 25.4% for patients with SNUC, 14.1% for patients with NEC, and 75.0% for patients with SmCC.

CONCLUSIONS. This spectrum of malignancies with neuroendocrine features shares a common site of origin within the head and neck, but their natural histories appear to diverge into two main groups: ENB and non-ENB. Patients with ENB had excellent local and distant control rates with local therapy alone. Given the higher rates of systemic failure for patients with SNUC, NEC, and SmCC, the authors favor the use of combined-modality therapy for these patients. ***Cancer* 2004;101: 2567–73.** © *2004 American Cancer Society.*

KEYWORDS: head and neck malignancies, neuroendocrine carcinoma, sinonasal carcinoma, survival.

Primary neuroendocrine tumors are uncommon head and neck malignancies that present with a varied histopathologic spectrum in sinonasal and nonsinonasal head and neck subsites. The nonsi-

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nonasal tumors are extremely rare,[1] but they generally have homogenous pathology, and patients with such tumors have poor outcomes.[2] The sinonasal tumors are more diverse, with four major histologic phenotypes: esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinoma (NEC), and small cell undifferentiated carcinoma (SmCC).[3] These tumors occur with enough frequency that specific treatment strategies have emerged.[4–7] We reviewed our institutional experience with sinonasal carcinomas with neuroendocrine differentiation (SCND) to determine whether there are distinct clinical characteristics warranting individualized treatment approaches.

MATERIALS AND METHODS

Patient Population

We reviewed the medical records of 72 adults who were treated for primary SCND of the head and neck at The University of Texas M. D. Anderson Cancer Center (UTMDACC) between 1982 and 2002. The patient population was identified through a search of the Tumor Registry data base maintained by the Department of Medical Informatics. All patients had newly diagnosed, nonmetastatic tumors arising from sinonasal head and neck subsites and were treated with curative intent. Patients who were seen at UTMDACC only for consultation or for treatment of recurrent disease were excluded. This retrospective review received Institutional Review Board approval, and patient data were maintained confidentially throughout the study.

Staging evaluation for these patients included history and physical examination, screening laboratory studies, chest X-ray, contrast-enhanced computed tomography (CT) scan or magnetic resonance image (MRI) of the head and neck, and biopsy of primary or lymph node disease in all patients. Abnormalities on chest X-rays were evaluated further (chest CT, biopsy) as necessary to exclude metastatic disease. All patients were restaged according to the new sinonasal staging system proposed by the sixth edition of the American Joint Committee on Cancer (AJCC) staging manual,[8] from documented clinical and pathologic findings.

Pathologic Analysis

Histopathologic slides prepared from archived blocks were reviewed, and immunohistochemical and electron microscopic findings were reevaluated by an experienced head and neck pathologist. Combined cytomorphologic and immunohistochemical features of neuroendocrine differentiation formed the basis for diagnosis. All tumors with small cells (well differentiated, moderately differentiated, and undifferentiated) that had positive staining for keratin, neuron-specific enolase, and chromogranin were included in this study. There were 31 patients with ENB, 16 patients with SNUC, 18 patients with NEC, and 7 patients with SmCC. Tumors that potentially could be confused with SCND (including paraganglioma,[10] basaloid squamous cell carcinoma,[11] melanoma,[12,13] pituitary adenoma/carcinoma,[14] and Merkel cell carcinoma[15]) were excluded from this analysis.

Statistical Analysis

Estimated rates of local failure, regional failure, distant failure, disease-free survival (DFS), and overall survival (OS) were calculated using the Kaplan–Meier method. Survival estimates were calculated from the date of diagnosis. Clinical and pathologic variables were assessed using the Mantel log-rank test for univariate analysis, and the Cox proportional hazards model was used for multivariate analysis. Retrospective categorization of late treatment toxicity was determined according to the National Cancer Institute's Common Toxicity Criteria, version 2.0 (which includes the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema).[16]

RESULTS

Patient Characteristics

The median age of the patients at the time of diagnosis was 48 years (range, 18–78 years), and a slight male predilection was noted (Table 1). No significant differences with regard to the median age or gender distribution were identified according to histopathologic subtype ($P = 0.69$). Racial distribution included 60 white patients, 2 black patients, 9 Hispanic patients, and 1 Asian patient. The majority of patients presented with locally advanced disease. The distributions according to the Tumor-Lymph Node-Metastasis (TNM) classification system and the AJCC staging system were as follows: Stage I disease in 2 patients, Stage II disease in 15 patients, Stage III disease in 10 patients, Stage IV disease in 42 patients, and unknown stage (TxN0) in 3 patients.

Treatment Characteristics

Treatment strategies are specified in Table 2. Because individual patient treatment strategies were determined according to multidisciplinary consensus during the 20-year study period, a variety of approaches are evident. In general, patients with ENB were treated with local therapy (surgery and/or radiotherapy) only to the primary tumor site; only 3 of 31 patients (9.7%) received treatment (radiation) to regional lymphatics, and only 5 of 31 patients (16.1%) received chemotherapy. In contrast, patients with non-ENB histologies usu

TABLE 1
Patient Characteristics

Characteristic	ENB	NEC	SNUC	SmCC	Total (%)
Gender					
Male	20	10	8	5	43 (60)
Female	11	8	8	2	29 (40)
Tumor classification					
T1	2	—	—	—	2 (3)
T2	11	2	2	—	15 (21)
T3	4	3	3	2	12 (16)
T4	14	10	11	5	40 (56)
Tx	—	3	—	—	3 (4)
Lymph node status					
N0	29	16	16	4	65 (90)
N1	1	1	—	2	4 (6)
N2	1	1	—	1	3 (4)
N3	—	—	—	—	0 (0)
AJCC Stage					
Stage I	2	—	—	—	2 (3)
Stage II	11	2	2	—	15 (21)
Stage III	3	3	3	1	10 (14)
Stage IV	15	10	11	6	42 (58)
Unknown	—	3	—	—	3 (4)

ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma; AJCC: American Joint Committee on Cancer.

TABLE 2
Primary Treatment Strategies Used to Treat Sinonasal Carcinomas with Neuroendocrine Differentiation at The University of Texas M. D. Anderson Cancer Center, 1982–2002

	No. of patients			
Treatment strategy	ENB	NEC	SNUC	SmCC
Surgery (with or without adjuvant RT/CT/CRT)	22/31	8/18	7/16	2/7
Preoperative RT (with or without adjuvant CT)	2/41	1/18	1/16	—
Primary RT or CRT (with or without adjuvant CT)	3/31	1/18	—	—
Induction CT → surgery or RT (with or without adjuvant/ concurrent CT	4/31	8/18	8/16	5/7

ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma; RT: radiotherapy; CT: chemotherapy; CRT: concurrent chemoradiotherapy.

ally received chemotherapy (10 of 16 patients with SNUC, 12 of 18 patients with NEC, and 5 of 7 patients with SmCC), and nonsurgical locoregional therapy was used more frequently (6 of 16 patients with SNUC, 4 of 18 patients with NEC, and 5 of 7 patients with SmCC).

OS and DFS

The median follow-up for surviving patients was 81.5 months (range, 6–266 months). The actuarial 5-year

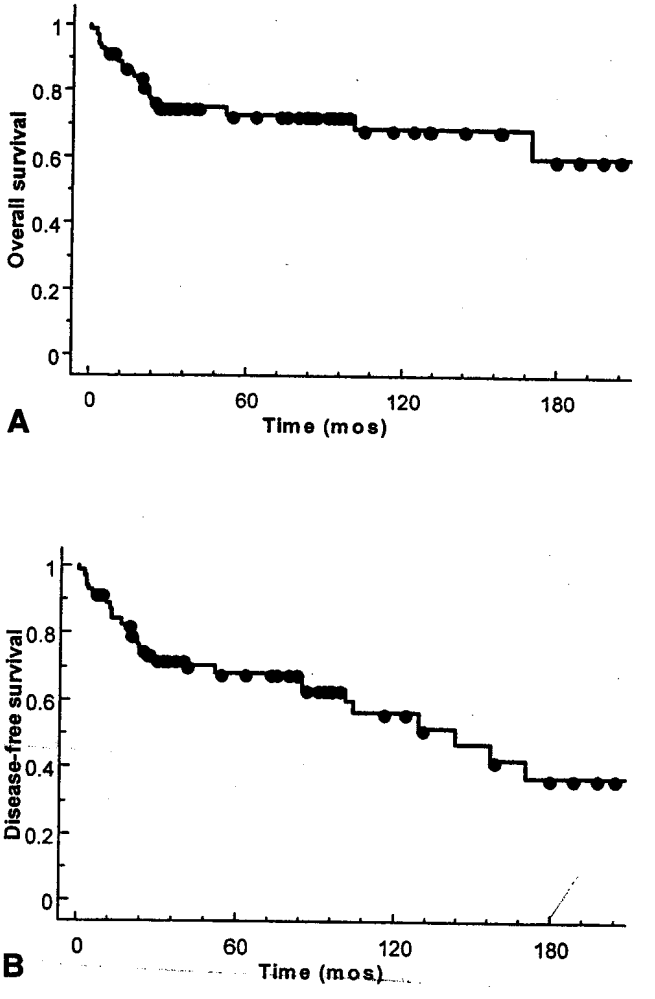

FIGURE 1. Overall and disease-free survival for all patients.

and 10-year OS rates were 72.8% and 68.8%, respectively; and the respective DFS rates were 68.2% and 56.3% for all patients in this series (Fig. 1). Statistically significant univariate discriminators of improved OS included tumor histology ($P = 0.0029$), age as a continuous variable ($P = 0.006$), and tobacco history ($P = 0.017$), and these factors remained statistically significant in the multivariate analysis (Table 3). Kaplan–Meier estimates of OS at 5 years were 93.1% for patients with ENB, 62.5% for patients with SNUC, 64.2% for patients with NEC, and 28.6% for patients with SmCC (Fig. 2).

Patterns of Failure

The 5-year and 10-year local control rates were 83.9% and 80.7%, respectively, for all patients; no additional local failures were noted after 7 years. The local control rate at 5 years was superior for patients who had ENB (96.2%) compared with patients who had SNUC

TABLE 3
Prognostic Factors for Survival: All Patients

Factor	No. of patients	5-yr OS (%)	*P* value	
			Univariate	Multivariate
Surgery (with or without Age (continuous variable)	72	N/A	0.006	0.02
Gender				
Male	43	69.7	0.38	—
Female	29	77.5		
Histology				
ENB	31	93.1	0.0029	0.02
NEC	18	64.2		
SNUC	16	62.5		
SmCC	7	28.6		
Lymph node status				
Negative	65	75.8	0.23	0.96
Positive	7	31.3		
AJCC stage				
Stage I–III	30	79.0	0.24	0.29
Stage IV	42	68.0		
History of cigarette use				
Yes	18	53.0	0.0175	0.005
No	54	79.6		

OS: overall survival; N/A: not applicable; ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma; AJCC: American Joint Committee on Cancer.

(78.6%), NEC (72.6%), or SmCC (66.7%; $P = 0.04$ for ENB vs. all other histologies) (Fig. 3).

The 5-year and 10-year regional control rates were 85.7% and 73.1%, respectively, for all patients. The regional failure rate at 5 years was 8.7% for patients with ENB, 15.6% for patients with SNUC, 12.9% for patients with NEC, and 44.4% for patients with SmCC ($P = 0.41$). Additional late events increased the regional failure rate for patients with ENB to 31.9% at 10 years. (Fig. 4).

The 5-year and 10-year distant metastasis rate was 15.3% for all patients. The distant metastasis rate at 5 years was 0.0% for patients with ENB, 25.4% for patients with SNUC, 14.1% for patients with NEC, and 75.0% for patients with SmCC ($P < 0.0001$) (Fig. 5). Three of four patients with SmCC who had distant failures developed brain metastases. The only long-term SmCC survivor (no evidence of disease at 14.2 years) was treated with prophylactic cranial irradiation integrated with his primary local radiation; all other patients with SmCC had died by 52 months.

Late Effects of Treatment

After combined-modality therapy, Grade 1–3 xerostomia (10 patients), Grade 1–2 serous otitis (3 patients), Grade 1–2 nasal obstruction (3 patients), Grade 1–3 ocular symptoms (dryness, irritation, corneal ulceration, and cataract; 5 patients), Grade 2 hypopituitarism (1 patient), Grade 2 cerebral necrosis (1 patient), and Grade 1–3 facial pain/trigeminal neuralgia (3 patients) were documented. A single patient suffered a myocardial infarction and died in the immediate postoperative period after undergoing craniofacial resection.

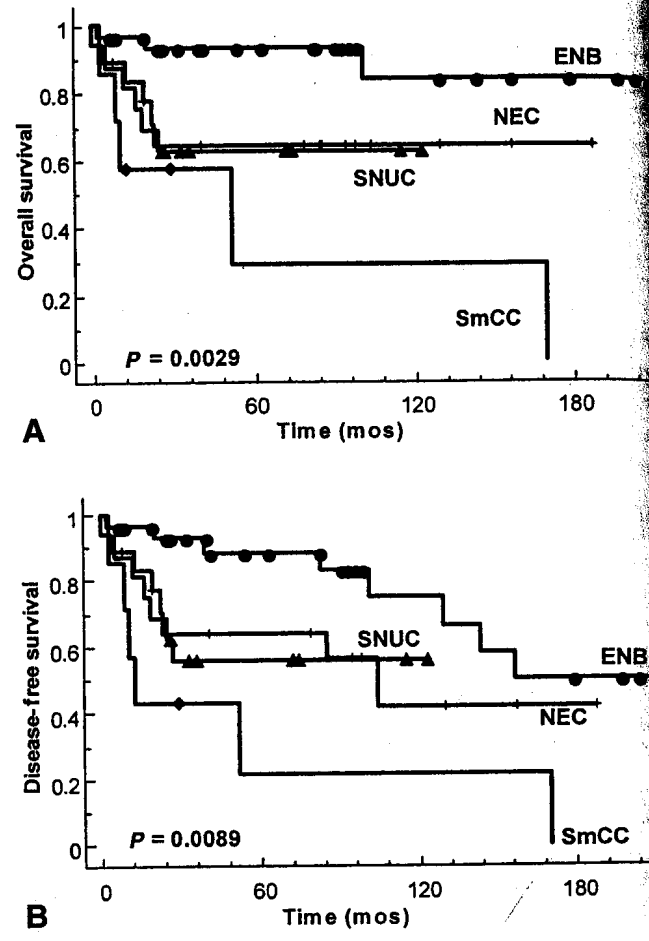

FIGURE 2. Overall and disease-free survival according to histopathologic subtype. ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma.

DISCUSSION

The current study data suggest that there are biologic differences among different types of SCND (Table 4). There appears to be a divergent natural history, which is divided macroscopically into ENB and non-ENB categories. Patients who have tumors with an ENB histology have excellent survival, local control, and distant control rates with local treatment only; in contrast, patients who have tumors with non-ENB histologies demonstrate poorer rates of survival that may be linked to the observed higher rates of systemic failure.

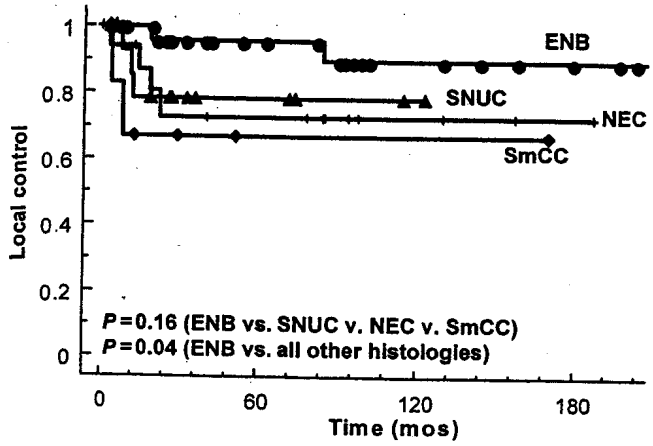

FIGURE 3. Local control according to histopathologic subtype. ENB: esthesioneuroblastoma; SNUC: sinonasal undifferentiated carcinoma; NEC: neuroendocrine carcinoma; SmCC: small cell carcinoma.

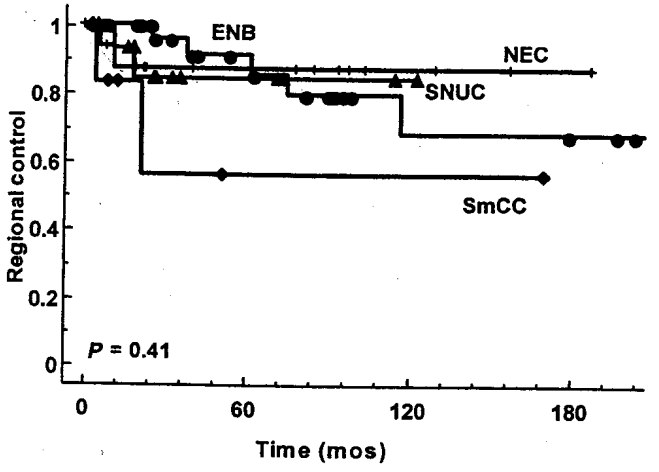

FIGURE 4. Regional control according to histopathologic subtype. ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma.

The strengths of the current retrospective review include strict inclusion criteria, comprehensive review of pathologic specimens (including immunohistochemistry for all patients) by one expert head and neck pathologist, and treatment of patients in the era of modern diagnostic imaging and pathologic analysis. Whereas many published series of SCND have included patients who were diagnosed in the 1970s or earlier, the current series included patients who were diagnosed and treated only after the use of electron microscopy and other advanced pathologic and immunohistochemical techniques were in routine use (early to middle 1980s). Nevertheless, this series included follow-up (median, 6.8 years) that was adequate for the natural history of these diseases.

To our knowledge, the majority of published series of ENB have emphasized local treatment strategies, and the combination of craniofacial resection and postoperative radiation therapy is recommended most frequently. Although older series that evaluated local therapy for patients with ENB resulted in local control rates $\leq$ 70%,[17] modern series of patients treated with craniofacial resection and postoperative radiation therapy have routinely resulted in local control rates of 86–96%.[6,7,18,19] Because the majority of patients with ENB continue to present with locally advanced disease (i.e., no significant stage migration seemingly has occurred during the past several decades), reported improvements in local control rates likely are due to advances in preoperative imaging, skull-base surgery, and adjuvant radiation therapy.

Delayed regional failures after local therapy for ENB have been reported previously.[20–22] In the current series, we also noted a finite rate of cervical lymph node metastasis after local therapy for ENB; and, unique to this histology, regional failures continued to

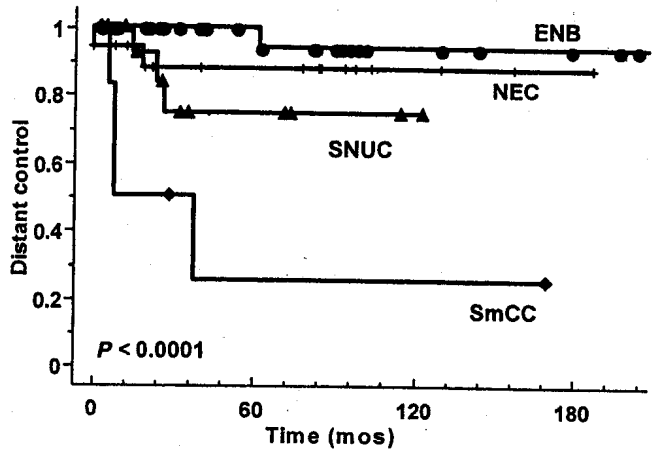

FIGURE 5. Distant control according to histopathologic subtype. ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma.

TABLE 4
Summary: Survival and Patterns of Failure in Patients with Sinonasal Carcinomas with Neuroendocrine Differentiation

	Five-yr rates (%)			
Histology	OS	LC	RF	DM
ENB	93.1	96.2	8.7	0.0
NEC	64.2	72.6	12.9	12.3
SNUC	62.5	78.6	15.6	25.4
SmCC	28.6	66.7	44.4	75.0

OS: overall survival; LC: local control; RF: recurrence-free; DM: distant metastasis; ENB: esthesioneuroblastoma; NEC: neuroendocrine carcinoma; SNUC: sinonasal undifferentiated carcinoma; SmCC: small cell carcinoma.

occur even after the often used 5-year benchmark after initial treatment. This clinical pattern was not evident in patients with the NEC, SNUC, or SmCC histologies, again suggesting a biologic difference between the ENB and non-ENB subtypes.

SNUC and NEC share virtually indistinguishable clinical outcomes but have differing morphologic and immunohistochemical characteristics. To our knowledge, no recent series to date have suggested significant differences in outcome between patients with SNUC and patients with NEC.

The earliest reported series of patients with SNUC suggested an overwhelmingly dismal outcome for these patients.[23,24] This appears to have been artifactual, however, because larger updated series have improved the outlook for patients with this disease.[25,26] The problem with the poor outcomes reported previously may have resulted from the lack of effective chemotherapy or the inclusion of small cell histologies.

Compared with patients who had ENB, both patients who had SNUC and patients who had NEC had higher rates of local failure (21–27% at 5 years). Higher rates of distant failure also were seen (12–25% at 5 years) despite the more frequent use of systemic therapy among these patients. These factors led to a significantly poorer OS for patients who had SNUC and NEC compared with patients who had ENB in this series.

SmCC is the least prevalent type of SCND. Although it is extremely limited, currently available information suggests that patients with these tumors have the highest rate of locoregional failure and distant metastasis, a finding that is supported by our series.[27] These tumors have been equated with anaplastic small cell carcinomas of the lung, and the high rate of intracranial metastasis (including intracranial metastasis as an isolated site of distant metastasis) supports this analogy. It is interesting to note that every patient with SmCC in the current series died from progressive disease within 4.5 years of diagnosis, with the exception of a single patient (demonstrating no evidence of disease at 14.2 years) who was treated with prophylactic cranial irradiation incorporated into the primary radiotherapy fields. Accordingly, we consider prophylactic cranial irradiation for selected patients with head and neck SmCC.[2]

Sinonasal malignancies with neuroendocrine features share a common site of origin within the head and neck, but their natural histories appear to diverge into two main groups: ENB and non-ENB. ENB has excellent local and distant control with local therapy alone, typically surgery and postoperative local RT. However, occasional late recurrences may be observed in the untreated neck, leading to individuation with regard to elective neck irradiation. Given the higher rates of systemic failure for patients with SNUC, NEC, and SmCC, we favor the use of systemic therapy in addition to radiation, depending on histology and response to chemotherapy and RT. However, to our knowledge, the recurrence rate for patients with SmCC remains high, despite a 100% initial CR rate, suggesting the need for newer and more effective therapies. Conversely, current combined modality approaches have resulted in good disease control and survival rates for patients with SNUC and NEC histologies.

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