ORIGINAL ARTICLE

Sinonasal malignancies with neuroendocrine differentiation: Case series and review of literature

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ABSTRACT

Primary sinonasal tumors with neuroendocrine differentiation (SCND) are uncommon tumors with considerable overlap of histological features. Based on their neuroendocrine differentiation they can be sub categorized into sinonasal undifferentiated carcinoma (SNUC), sinonasal neuroendocrine carcinoma (SNEC), esthesioneuroblastoma (ENB) and small cell carcinoma (SmCC). The natural history and biological behavior varies in this group of tumors. Hence the histo-morphological diagnosis coupled with grading/staging is important for the prognostication of these tumors. **Aim**: To study the clinicopathological characteristics of sinonasal neuroendocrine malignancies at our institute. **Material and Methods**: We searched our institute's pathology database for the period from 2002 to 2007, for the four subcategories of sinonasal tumors with neuroendocrine differentiation. Morphological and immunohistochemical features were studied and, grading, staging was done in accordance with standard criteria. The clinical treatment and follow- up data were retrieved from the case files in available cases. **Results**: A total of 37 cases were retrieved from our database which include 14 cases of SNUC, 14 cases of ENB and nine cases of SNEC. The cases of SNUC were immunopositive for cytokeratin, epithelial membrane antigen and weakly for neuron-specific enolase. SNEC showed strong reactivity with epithelial and neuroendocrine markers whereas ENB demonstrated immunoreactivity to synaptophysisn and chromogranin strongly, with weak to negative expression of epithelial markers. All cases of SNUC and SNEC were of high grade and stage whereas 50% of ENB cases were of grade II but high stage tumors. Most of the SNUC and SNEC patients had been treated with multimodality treatment regimens including upfront chemotherapy followed by surgery and loco- regional radiation. In contrast, ENB patients had undergone surgical extirpation followed by radiation therapy in majority of cases. With limited follow-up data, it was observed that four out of five SNUC patients and three out of four SNEC patients developed either loco-regional (three of SNUC and two of SNEC) or distant metastasis (one patient each of SNUC and SNEC). ENB patients also had loco-regional recurrences (five out of seven patients) with a more protracted course but no distant metastases were observed during the follow up in available cases.**Conclusion**: Sino nasal tumors with neuroendocrine differentiation are a heterogenous group of tumors with overlapping histo-morphological features. They can be distinguished based on immunohistochemical characteristics. Pathological sub categorization is imperative for management and prognostication of these aggressive tumors.

KEY WORDS: Carcinoma, esthesioneuroblastoma, neuroendocrine, Sinonasal

DOI: 10.4103/0377-4929.59179

INTRODUCTION

Malignant tumors of the sinonasal tract comprise less than one per cent of all neoplasms and three per cent of those of the upper aerodigestive tract.[1,2] Sinonasal malignancies are aggressive tumors as they present at a late stage and are difficult to treat; potential therapy includes mutilating surgery.

Primary sinonasal neuroendocrine tumors are uncommon head and neck tumors with a varied histopathologic spectrum. These are diverse and four histologic phenotypes are recognized: esthesioneuroblastoma (ENB), sinonasal undifferentiated carcinoma (SNUC), sinonasal neuroendocrine carcinoma (SNEC) and small cell undifferentiated carcinoma (SmCC). They differ in cell of origin, degree of neuroendocrine differentiation and biologic behavior. SmCC, SNUC, SNEC (together referred to as non-ENB) and ENB can be conceptualized as being part of a spectrum of neuroendocrine-type tumors, with esthesioneuroblastoma representing the most differentiated end of spectrum of neuroendocrine tumors and SmCC represents the most undifferentiated end.[3-5] There is considerable overlap between the histopathologic features of these tumors, which may complicate their diagnosis.[5,6]

The grading and staging of these tumors is unique and prognostically important.[7-11] Modern imaging modalities delineate the local extent of tumor. They indicate the malignant nature of the mass but do not help in differential diagnosis. Given the difference in treatment and prognosis of these histologic entities, correct diagnosis is essential. We have, in this study, reviewed our institutional experience with this group of tumors highlighting

the clinicopathological characteristics and diagnostic features.

MATERIAL AND METHODS

The pathology database system of our hospital from 2002 to 2007 was searched for patients with a diagnosis of ENB, SNUC, SNEC and SmCC. A total of 37 cases were retrieved from the database. Our institutes being a tertiary cancer center, most of the cases were of referral type and only stained slides were available for review. The histopathological and immunohistochemical characteristics, wherever available were reviewed. Additional IHC was done in required cases, to further delineate these tumors.

SNUC was diagnosed wherein tumor cells were either small or large and were arranged predominantly in nests, ribbons and thick trabeculae or sheet-like pattern and had coarse chromatin and prominent nucleoli. Numerous mitosis, apoptosis, vascular invasion and comedo type necrosis were also seen in majority of tumors. On immunohistochemistry, these expressed cytokeratin (CK) and/or epithelial membrane antigen (EMA) and weak neuron specific enolase (NSE).

A tumor was classified as SNEC if cells were dispersed in sheets or ribbons and trabeculae with perivascular rosettes were seen focally. However, true rosetting or neurofibrillary background was absent. The nuclear chromatin was fine "salt and pepper like" or homogenous granular quality. Nucleoli, if present, were inconspicuous. These tumors expressed one or more of the neuroendocrine markers diffusely {chromogranin (CHR), NSE, synaptophysin (SYN)} in addition to the epithelial markers.

ENB was characterized by the presence of sharply defined nests of discohesive cells with small round appearance separated by interlobular fibrovascular stroma along with background neuropil, Homer-Wright rosettes and sustentacular cells. Radiological records of involvement of cribriform plate and strong positivity for chromogranin and/or synaptophysin, in the absence of CK and EMA further confirmed the diagnosis of ENB. On review, one case of SNEC was re classified as ENB. Hence after review, 14 cases of SNUC (37.8%), 14 cases of ENB (37.8%) and nine cases of SNEC (24.3%) were identified. There were no cases of primary small cell carcinoma of the sino nasal tract found in our records. Information regarding patient demographics, treatment regimens and outcomes were gathered from the medical records of the patients in available cases. The Kadish (Morita modification)[12] staging system was applied for all cases and Hyams grading[7] was assigned on histopathological slides. [Tables 1 and 2]

Table 1: Salient Features of Criteria for Hyams Histologic Grading

Histologic criteria	*Grade I*	*Grade II*	*Grade III*	*Grade IV*
Lobular architecture	++	+	_	_
Neuropil	++	+	+/-	_
Rosettes	+/-	+/-	+/-	_
Necrosis	_	_	+	++
Nuclear Pleomorphism	_	+	++	+++

RESULTS

Patient Demographics

There were 37 patients (30 men, seven women) with tumors; SNUC (14), SNEC (nine) and ENB (14). In ENB patients, the age ranged from 10 to 54 years (mean 41.5y) where as for non-ENB the range was 20 to 72 years (mean 50.8y). In all cases of ENB the superior nasal cavity/ethmoid including cribriform plate was involved. The predominant site was nasal cavity with/without maxillary involvement (seven SNUC and eight SNEC) in non-ENB cases. The sphenoid sinus (one case), nasopharynx (two cases) and ethmoid sinuses (two cases) were the other predominant site in rest of the cases of SNUC. At presentation, cervical lymph node metastasis was seen in one case of SNUC, two cases of SNEC and two cases of ENB. All cases of SNUC and SNEC were of either Hyams grade III or IV and most of them were of Kadish stage B or C. Most cases of ENB were of Hyams grade II (seven cases) and Kadish stage C.

Histopathology and Immunohistochemistry

Of the 14 cases of sino nasal-undifferentiated carcinoma [Figure 1a-d], morphologically the majority of tumors had a predominant sheet-like pattern in 10 cases. Numerous mitosis, apoptosis and abundant necrosis were seen in all cases. Vascular invasion was seen in eight cases. Comedo type necrosis was seen in five cases.

Of the nine cases of SNEC [Figure 2a-d], the cells were dispersed in thick trabecular and ribbon like pattern in five cases whereas a prominent sheet like arrangement was appreciated in four cases. pseudo rosettes were seen focally in six tumors. "Salt and pepper like" nuclear quality was seen in seven out of nine cases; homogenous granular quality in two. In five cases of SNUC and four cases of SNEC the tumor had an associated dense lymphocytic infiltration.

In ENB [Figure 3a-d], nests and lobules of small sized cells were seen in eight of the 14 cases separated by interlobular fibrovascular stroma. The presence of neuropil and Homer-Wright rosettes was noted in six cases. There were six cases with were high grade nuclei (three cases Hyams grade III and 3 were Hyams grade IV) and the mitotic figures were frequent. In these cases the tumor cells superficially resembled the cells of SNEC. But the focal rosettes and smaller size of cells helped in arriving at the diagnosis on H and E sections. Paraffin blocks were available in 18 out of 37 cases (three out of 14 cases of SNUC, six out of nine cases of SNEC and nine out of 14 cases of ENB) and the immunohistochemical profile of these tumors is tabulated in Table 3.

Table 2: Morita Modification of Kadish Staging

Stage A –	tumor involving nasal cavity
Stage B –	tumor involving paranasal sinuses
Stage C –	tumor extending beyond nasal and paranasal sinuses to involve cribriform plate, skull base, orbit or intracranial cavity
Stage D (Morita modification)	– tumor metastatic to cervical lymph nodes or distant metastasis

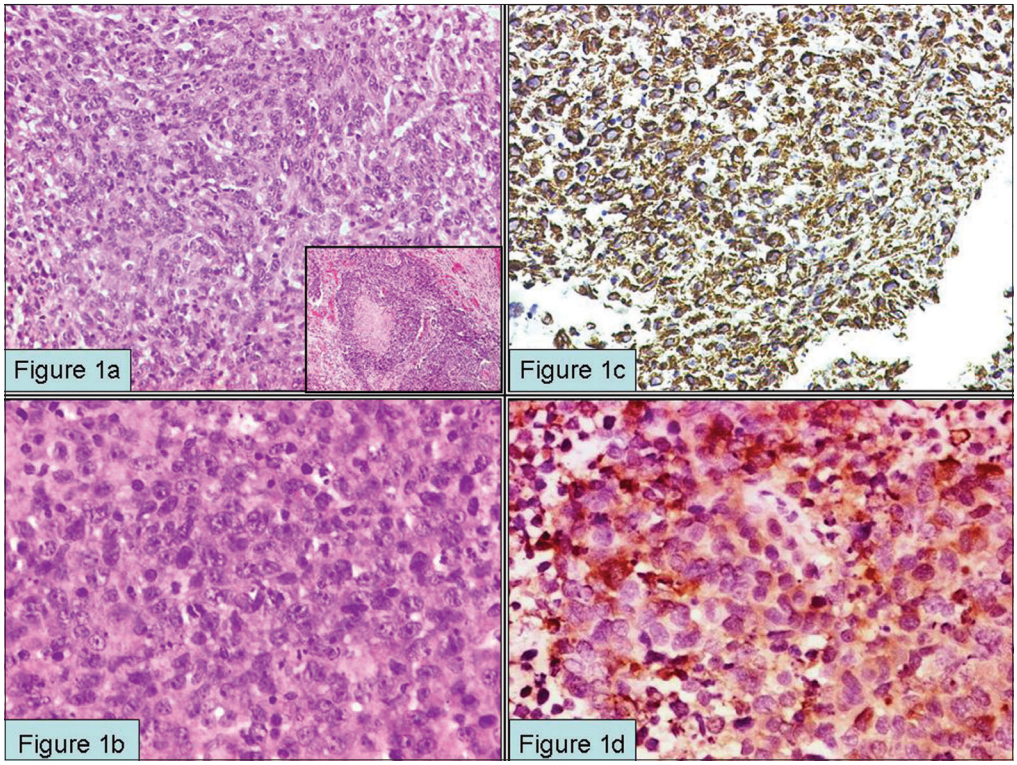

Figure 1: Sino nasal undifferentiated carcinoma: Sheets of oval to spindly cells admixed with lymphoid cells. Inset shows comedo-necrosis pattern [fig 1a] (H and E; x100). The undifferentiated cells have prominent nucleoli, abundant apoptosis [fig 1b] (H and E; x200). Tumor cells show immunoreactivity with cytokeratin and weakly with neuron-specific enolase (figure 1c and 1d respectively; IHC;x 200)

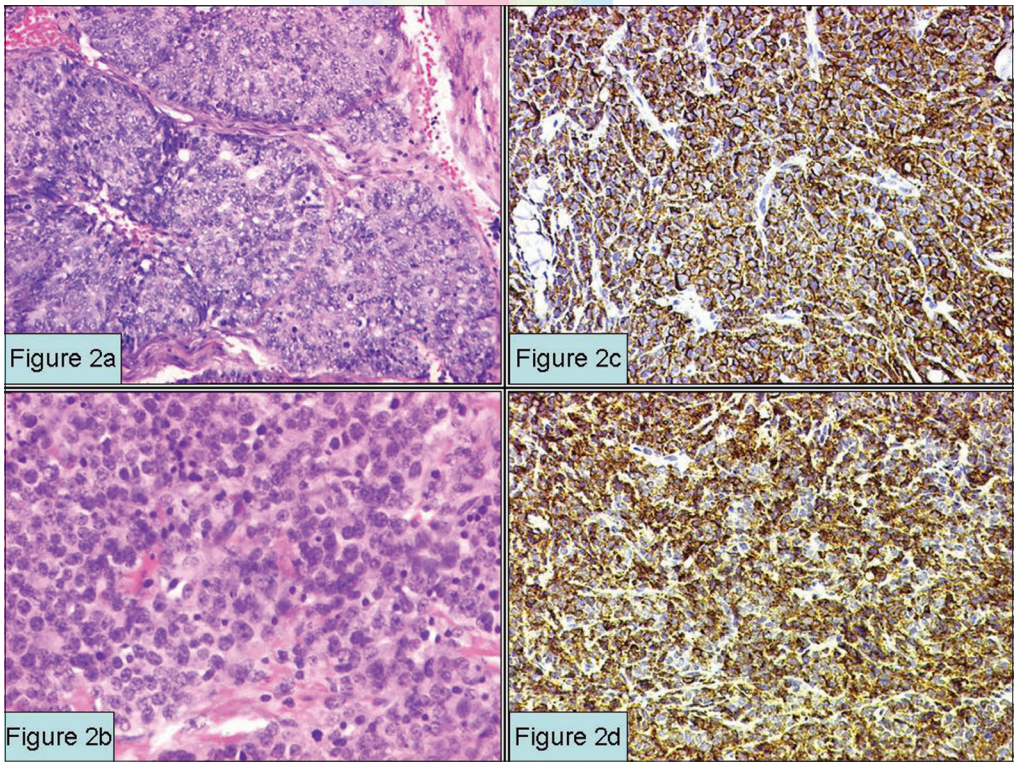

Figure 2: Sino nasal neuroendocrine carcinoma: The malignant cells are dispersed in vague lobular pattern with focal rossete-like arrangement [fig 2a] (H and E; x100). The cells have salt and peppery chromatin and demonstrate apoptosis [fig 2b] (H and E; x200). Tumor cells show immunoreactivity to cytokeratin and strongly to chromogranin (fig 2c and 2d respectively; IHCx200)

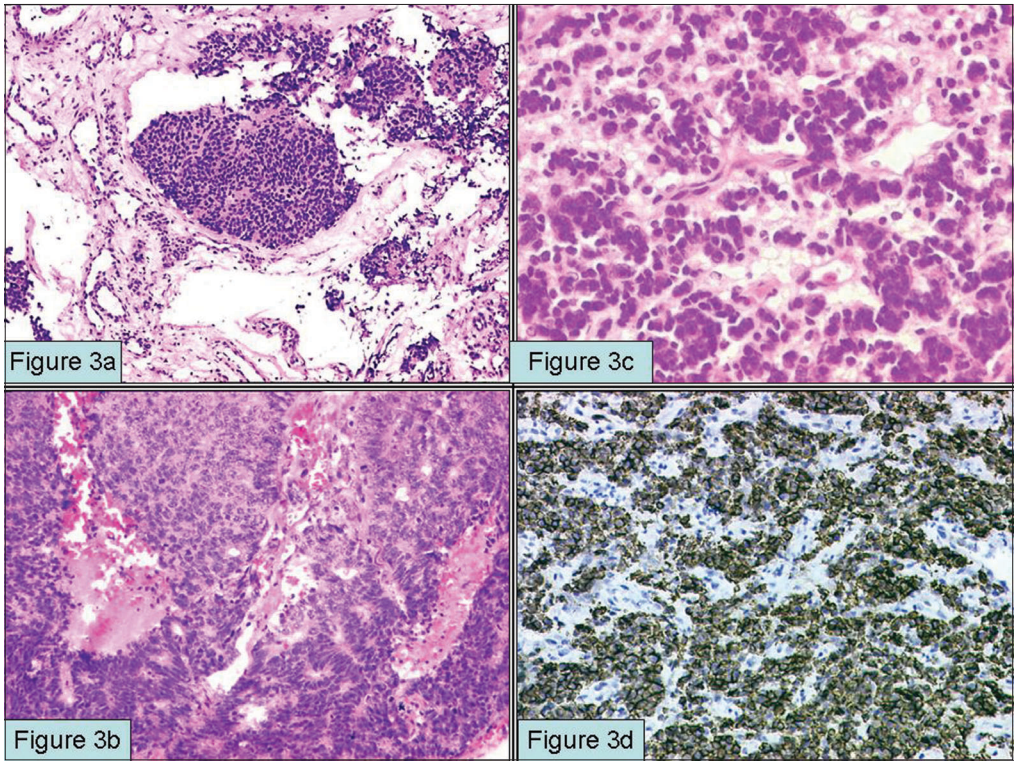

Figure 3: Esthesioneuroblastoma: Tumor cells are arranged in lobules separated by vascular and desmoplastic stroma [fig 3a] (H and E; x4). Tumor cells show rossette formation and may have comedonecrosis pattern [fig 3b] (H and E; x100). Higher grade tumors of Hyams III and IV grade with cord and trabecular pattern comprised of blue undifferentiated cells in a fibrillary background [fig 3c] (H and E; x200). Tumor cells show immunoreactivity for synaptophysin

Table 3: Immunohistochemical Profile in Sino Nasal Neuroendocrine Tumors

Patient No.	*Diagnosis*	*CK*	*EMA*	*NSE*	*CHR*	*SYN*	*S-100*	*Other markers*
1	SNUC	+	+	+	-	-	-	
2	SNUC	+	+	Weak+	-	-	NT	
3	SNUC	+	+	+	-	-	NT	
4	SNEC	+	+++	Weak+	+	++	-	-LCA
5	SNEC	+	+++	NT	++	+	-	
6	SNEC	+	++	+	+	+	-	
7	SNEC	+	+++	NT	Weak +	++	NT	
8	SNEC	+	++	NT	+	++	-	
9	SNEC	+	+++	-	+	++	NT	-LCA
10	ENB	-	-	-	Weak+	+	+	-DES,-MyoD1
11	ENB	-	-	NT	NT	+	+	-DES,
12	ENB	-	-	NT	NT	+++	Weak +	-LCA
13	ENB	-	-	-	+	Weak+	-	-LCA
14	ENB	-	-	-	Weak+	+	Weak+	
15	ENB	-	-	-	Weak+	-	Weak+	
16	ENB	-	-	-	+	+	+	
17	ENB	-	-	-	+	+	+	
18	ENB	-	Weak+	-	+	+	Weak+	

CK=cytokeratin; EMA=epithelial membrane antigen; NSE=neuron-specific enolase; SYN=synaptophysin; CHR=chromogranin; LCA=leucocyte common antigen; Des=desmin; NT=not tested

Treatment and Follow-up

The treatment and follow-up data was limited and available in only 16 out of 37 cases (five out of 14 cases of SNUC, four out of nine cases of SNEC and seven out of 14 cases of ENB).

In general, ENB patients were treated with local therapy (surgery plus local RT). Only two out of seven patients of ENB who were inoperable at presentation had received systemic chemotherapy and radiation to involved regional nodes. Upfront chemotherapy was given to four out of five patients with SNUC and two out of four cases of SNEC. Loco regional radiotherapy was given to all cases of SNUC and SNEC.

The mean follow-up of all cases together was 11.5 months (range from 2 to 56 months). Clinical course and outcome are depicted in Table 4. Recurrences were seen in majority of SNUC patients (four

Table 4: Patient Demographics, Treatment Modalities and Follow-up

S. No.	*Diagnosis*	*Age/Sex*	*Tumor site*	*Hyams grade/ Kadish stage*	*LN*	*Treatment*	*Recurrence /Mets Site (Mo)*
1	SNUC	35/F	M and N	IV, C	-	CT + RT	Local (5 mo)
2	SNUC	45/M	M and N	IV, C	-	CT + RT	Distant (8 mo)
3	SNUC	49/M	N and E	III, B	-	Sx+ CT +RT	Local (5 mo)
4	SNUC	61/F	N and M	III, C	-	Sx+ RT	Regional (8mo)
5	SNUC	43/M	N and S	IV, D	+	CT + RT	None
6	SNEC	60/M	N and M	IV, C	-	CT + RT	None
7	SNEC	34/M	N, S and E	III, D	+	Sx + RT	Loco regional (13 mo)
8	SNEC	46/M	N and E	IV, B	-	Sx + RT	Loco regional (8 mo)
9	SNEC	20/M	N, M and E	IV, D	+	CT + RT	Distant (4 mo)
10	ENB	19/M	N andE	II, B	-	Sx+ RT	Local (15 mo)
11	ENB	45/F	N and E	I, C	-	Sx+ RT	None
12	ENB	10/M	N and E	III, C	-	Sx+ RT	Local (2 mo)
13	ENB	54/M	N and E	III, C	-	Sx + Rt	Local (7 mo)
14	ENB	42/F	N and E	II, D	+	Sx + RT+CT	None
15	ENB	45/M	N and E	II, C	-	Sx+ RT	Regional (12 mo)
16	ENB	50/M	N and E	III, D	+	Sx +RT+CT	Loco regional (24and50mo)

N=nasal cavity; M=maxillary sinus; E=ethmoid sinus; S=sphenoid sinus; Sx=surgery; RT= radiation therapy; CT= chemotherapy.

out of five). Two had local recurrence, one had CSF metastasis and one developed regional nodal metastasis. In patients with SNEC, two out of four patients had local recurrences and one developed multiple bony metastases. The patient of SNUC with CSF metastasis and SNEC with bone metastasis died of the disease.

ENB patients had a more protracted course of events with five out of seven developing either local or regional recurrence two to 50 months after diagnosis. Two patients had no evidence of disease at seven and 12 months.

DISCUSSION

Sinonasal neuroendocrine malignancies are diverse, complex and uncommon, yet very aggressive tumors. The aggressiveness of these tumors is partly due to the complex anatomy of this site, with close proximity to vital structures coupled with delayed presentation of patients due to non-specific symptoms, which preclude radical surgical extirpation and radiation therapy.[1-4] In a study by Silva *et al.*[13] the mean age of patients of SNEC was 50 years and that for ENB was 20 years. However, other studies have shown a bimodal age distribution of ENB with median age of 49 years. We found that the mean age of our non-ENB patients (SNUC, SNEC and SmCC) 50.8 years while that for ENB was 41.5 years.

Histopathology and Prognostic Systems

Although there is considerable overlap of histopathologic features of SNUC, SNEC and ENB, a correct preoperative biopsy diagnosis can be made in most cases on light microscopic features alone.[5,6] The important histopathological parameters which help in differentiating these tumors include the pattern of tumor cell arrangement, stroma, nuclear chromatin character, presence or absence of neuropil and rosetting. Immunohistochemistry is crucial in arriving at exact categorization in difficult situations.[14,15] Other entities like Non-Hodgkin's lymphoma, primary melanoma and rhabdomyosarcoma can occur at this site and cause considerable diagnostic confusion. Clinical, radiological and immunohistochemical evidence can help in the differential diagnosis. In addition to the aforementioned epithelial and neuroendocrine IHC markers, the use of appropriate immunohistochemical stains including LCA, desmin and S-100 helped us in differentiating sinonasal neuroendocrine tumors from these entities. Resemblance to nasopharyngeal type of carcinomas was striking in some of the cases in our study, owing to the intricate admixture of lymphocytes with the malignant cells. However, the tumor cells lacked characteristic vesicular nuclei and the large nucleoli of nasopharyngeal carcinoma and there was no involvement of nasopharynx in these cases.

There is no uniformly accepted prognostic system for prognostication of sinonasal neuroendocrine malignancies. The pathologic grading system for esthesioneuroblastoma was developed by Hyams[7] who, based on histologic features (lobular architecture, neuropil, rosettes, nuclear pleomorphism and necrosis), divided them into four grades with grade I tumors having excellent prognosis and grade IV with uniformly fatal outcome. This system has been found to correlate with prognosis in other studies also.[8,9] Miyamoto demonstrated the prognostic importance of this system by extending this grading system to SNUC.[10] For staging purposes, the best known and widely used system is that devised by Kadish [11]and modified by Morita[12] to include tumors with cervical lymph node or distant metastasis under stage D. In our study, we have graded all our tumors using Hyams grade as these tumors can be conceptualized to be a part of neuroendocrine tumor spectrum. Our cases of SNUC and SNEC were all of Hyams grade III or IV and presented at a higher stage. Six patients of ENB patients had also presented as higher stage tumors even though most of them were of Hyams grade II. We found that grade III and IV tumors and higher Kadish stage of any histologic type behaved aggressively indicating the general trend of poor behavior.

Treatment and Outcome

The rarity of these tumors has allowed only a few treatment and prognostic comparisons among SNUC, SNEC, SMCC and ENB. In 2004, Rosenthal *et al.*[4] studied the patterns of failure in SCND according to histologic phenotypes. The authors concluded that

based on their behavior and natural history SCND can diverge into two main groups: Esthesioneuroblastoma (ENB) and non–ENB. This categorization is based on the fact that excellent loco-regional and distant control of ENB can be achieved with local therapy alone (surgery plus/minus postoperative local RT) whereas SNUC, NEC and SmCC have higher rates of local and systemic failure and hence require an aggressive multimodality approach including upfront chemotherapy.[3,4]

Cases of SNUC and SNEC in this study were treated with a multimodality approach with surgery and/or chemotherapy followed by radiotherapy to the local site and neck. On the other hand ENB cases were treated primarily with surgical extirpation followed by local radiation to the primary site. Only cases presenting with nodal metastases were given upfront chemotherapy in patients of ENB.

The outcomes for SNUC and SNEC are generally reported to be poor. Loco-regional recurrences have been reported as high as 63% in study of SNUC by Kim *et al*.[6] In the original report by Frierson *et al*.[16] the median survival was only four months in patients of SNUC treated with radiotherapy alone. Improved survival (median 53.6 months) results for SNUC were reported by Deutsch *et al*.[17] by using aggressive multimodality approach. Silva *et al*.[13] reported 20 patients of SNEC with a high propensity to metastasize to lymph nodes, brain and bone. Rosenthal *et al*.[4] reported promising results in 2004 with overall five year survival rate of 93.1% for ENB, 64.2% for SNEC and 62.5% for SNUC.

In our series, even with radical treatment we found that four out of five patients of SNUC and three out of four patients of SNEC developed recurrent disease. The median time to recurrence was eight months. Most of the recurrences were local with extention into cranial cavity and involved temporoparietal lobe. One case of SNUC recurred in the regional node and two cases of SNEC recurred locally as well as in draining lymph nodes. One patient each of SNUC and SNEC died of metastatic disease to spinal cord and bones respectively.

The reported loco-regional recurrence rate in ENB ranges from 27 to 62% with most recurrences within first two years of diagnosis.[8,18] Local/loco regional recurrence was seen in five out of seven patients of ENB in this series with median time of 12 months. One patient had loco-regional recurrence at 24 and 50 months. In this patient the recurrences responded well to chemo-radiation. The higher recurrence rate in cases of ENB in our series may be because most of our follow-up cases were of Hyams grade III and stage C which independently connote a poorer outcome. None of the patients of ENB had distant organ metastasis during the period of follow-up.

Based on the follow-up of limited number of cases, no definite conclusions regarding survival pattern was possible in our study, although the overall poor behavior of these tumors is well demonstrated. As previously mentioned, most of the patients in this series were referred to our tertiary cancer care center after partial and inadequate management. This factor might have led to a compromise in planning and execution of further radical management with a consequent poor outcome.

In conclusion, this study highlights the characteristics of sinonasal neuroendocrine malignancies and emphasizes the importance of immunohistochemistry in distinguishing ENB from non-ENB. We conclude that this group of tumors is highly aggressive and even with multimodality approach to treatment the outcome is generally poor. Larger prospective series, with research to develop newer effective treatment, including targeted therapy, should improve outcome in future.

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Source of Support: Nil, **Conflict of Interest:** None declared.