



# Esthesioneuroblastoma and Sinonasal Undifferentiated Carcinoma: Impact of Histological Grading and Clinical Staging on Survival and Prognosis

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**Objectives:** Hyams proposed a histological grading system for esthesioneuroblastoma in which grade I tumors have an excellent prognosis and grade IV tumors are uniformly fatal. The Hyams grading system predated advanced craniofacial techniques, extensive use of immunohistochemistry, and the recognition of sinonasal undifferentiated carcinoma (SNUC) as a distinct entity. Therefore we aimed to determine whether Hyams classification is useful in predicting outcome for esthesioneuroblastoma and SNUC. **Study Design:** A retrospective review of cases from 1970 to 1999. **Methods:** Twenty-six patients (12 with esthesioneuroblastoma and 14 with SNUC) were reviewed. The Kadish clinical stage was determined, and histopathological slides were reviewed and graded using the Hyams system. **Results:** Kadish staging was available for 26 patients (2 patients with stage A tumors; 7 with stage B; and 17 with stage C). Of the 8 evaluable patients with Kadish stage A or B tumors, 6 remained disease free for more than 2 years compared with only 5 of the 17 Kadish stage C tumors. Slides were available for Hyams grading in 21 patients (2 patients with grade I tumors; 4 with grade II; 4 with grade III; and 11 with grade IV). Of the 6 patients with Hyams grade I or II tumors, 4 remained disease free for more than 2 years compared with only 4 of the 15 patients with Hyams grade III or IV tumors. Of note, three patients with Kadish stage C tumors (two with esthesioneuroblastoma, one with SNUC) and two patients with Hyams grade IV tumors (one with esthesioneuroblastoma and one with SNUC) survived for more than 5 years. **Conclusions:** Both the Hyams grading system and the Kadish staging system

can be used as independent predictors of outcome. Although limited by small numbers, the results of this study demonstrate that patients with either advanced clinical stage or pathological grade of esthesioneuroblastoma or SNUC have poor prognosis, but that long-term survival is possible in these patients if aggressive treatment is used. **Key Words:** Esthesioneuroblastoma, sinonasal undifferentiated carcinoma, pathological staging, histological grading.

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## INTRODUCTION

Esthesioneuroblastoma is an uncommon sinonasal tumor, and sinonasal undifferentiated carcinoma (SNUC) is a related tumor that only recently was recognized as a distinct entity.<sup>1</sup> SNUC has a poorer cure rate than esthesioneuroblastoma.<sup>1-3</sup> Some esthesioneuroblastomas are very aggressive, whereas there are some SNUC tumors that can be cured.<sup>3</sup> Prognostic factors have been examined for esthesioneuroblastoma, but there is no agreement as to which is most useful.<sup>4-8</sup>

Hyams developed a pathological grading system classifying esthesioneuroblastomas into four grades based on histological features. This grading scheme reportedly provides prognostic information, with grade I patients having a uniformly good outcome and grade IV patients all dying of disease.<sup>9</sup> Kadish similarly devised a clinical staging system.<sup>10</sup> No system has been specifically described for SNUC, but Hyams grade IV includes features consistent with SNUC.<sup>1,9</sup> This study reviews our center's experience with these tumors to investigate the utility of the Hyams grading and the Kadish staging systems for prognosis.

## MATERIALS AND METHODS

The Head and Neck Tumor Registry at the University of Cincinnati Medical Center from 1970 to 1999 was reviewed for patients with primary esthesioneuroblastoma or SNUC. The patients described in a prior review of SNUC at our institution were included.<sup>3</sup> Twenty-six patients were identified; 12 of these patients were classified as having esthesioneuroblastoma on histological and immunohistochemical examination, and 14 as having

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TABLE I.  
Patient Information.

Age (y)	Sex	Metastases	Kadish/Hyams Grade	Surgery	XRT (Gy)	CTX	Recurrence or Persistence			Outcome (Total Months Survived)
							Months	Site	Treatment	
<b>Esthesioneuroblastoma Patients</b>										
53	F	0	C	CFR/OE	0	N	2	Local	Surg/XRT	DOD (4)
85	M	0	IV	WLE	63.0	N	NA			Dead, ICD (118)
71	F	0	I	WLE	0	N	NA			Alive, NED (70)
70	F	+	N/A	CFR/ND	64.8	N	23	Local	None	DOD (38)
59	F	0	C	WLE	59.4	N	46	Dist	XRT	DOD (56)
35	M	+	C	CFR	66	Y	NA			Alive, NED (17)
28	M	0	II	CFR	89.7	Y	19	Reg	Surg	DOD (31)
17	M	0	III	CFR	67.84	N	26	Local	CTX	Alive, NED (91)
53	F	0	III	WLE	60	N	59	Reg	Surg	DOD (131)
82	F	0	IV	CFR	0	N	100	Reg	XRT/CTX	Dead, PE (1)
33	F	+	I	CFR/ND	59.4	N	46	Dist	None	DOD (85)
25	M	0	II	CFR	55.8	N	NA			Alive, NED (71)
			I							
<b>Sinonasal Undifferentiated Carcinoma Patients</b>										
55	M	0	C	CFR/OE	59.4	N	2	Local	Surg/XRT	DOD (29)
76	M	0	IV	CFR	59.4	N	NA			Dead, ICD (34)
45	M	0	IV	0	54.0	Y	NA			Alive, NED (71)
75	M	0	IV	CFR/OE	64.8	N	6	Local	None	DOD (6)
44	M	0	B	CFR	60	N	179	Local	Surg	Alive, NED (195)
36	M	0	N/A	0	66.6	Y	7	Local/dist	CTX	DOD (22)
22	M	+	III	0	70	Y	12	Dist	CTX/XRT	DOD (13)
83	M	0	IV	WLE	0	N	1	Local	None	DOD (17)
41	F	0	A	0	66.6	Y	NA			Dead, ICD (24)
49	M	+	N/A	CFR/OE/ND	61.4	Y	6	Local/dist	CTX/XRT	DOD (8)
52	M	0	IV	CFR/OE	0	N	0			DOD (1)
68	M	0	C	WLE	46	N	0			Alive, NED (43)
47	M	0	B	CFR/OE	59.4	N	0			Alive, NED (18)
65	M	0	N/A	0	66.6	Y	0			Alive (3)
			IV							

0 = no regional metastases present; + = regional metastases present; N/A = Hyams grading not available; WLE = wide local excision; CFR = craniofacial resection; CFR/OE = craniofacial resection with orbital exenteration; ND = neck dissection; XRT = radiation therapy; CTX = chemotherapy (agents used included 5-FU, cisplatin, VP16, cytoxan, adriamycin; Y = chemotherapy given; N = no chemotherapy given); Months = months until recurrence; local = local recurrence; dist = distant recurrence; reg = regional recurrence; Surg = surgery; NA = not applicable; DOD = dead of disease; ICD = intercurrent disease; NED = no evidence of disease; PE = pulmonary embolism in postoperative period.

SNUC. The patients with esthesioneuroblastoma included 7 female and 5 male patients, with ages ranging from 17 to 85 years (mean age, 51 y). Patients with SNUC included 1 female patient and 13 male patients with ages ranging from 22 to 83 years (mean age, 54 y). All cases were reviewed with attention to treatment, recurrence at primary, regional or distant sites, overall survival, and disease-free survival. Surgical treatment ranged from medial maxillectomy and ethmoidectomy with tumor excision in the earlier cases to craniofacial resection, which is the current standard.

The Kadish stage was determined by review of the patient records, which were available for 26 patients. The histopathological slides, which were available in 22 patients, were reviewed by a head and neck pathologist (P.W.B.) who was blinded to the diagnosis, treatment, and survival data. The same histopathological parameters used by Hyams to evaluate esthesioneuroblastoma were also applied to the SNUC cases for assigning Hyams grades to both tumor types. These parameters included lobular architecture, neurofibrillary matrix, rosettes, nuclear pleomorphism, mitotic activity, necrosis, and calcification. Survival was analyzed by Fisher's Exact Test and the Kaplan-Meier method.

## RESULTS

Treatment consisted of surgery alone in 5 patients, surgery followed by irradiation in 12 patients, irradiation followed by surgery in 1 patient, and chemoradiation therapy in 7 patients, 2 of whom underwent surgery after response to treatment (Table I).

Recurrence occurred in 6 of the 12 patients with esthesioneuroblastoma. The recurrences were local in two patients (frontal lobe; nasal cavity, nasal vestibule, and meninges), regional in two patients (cervical lymph nodes), and distant in two patients (lung and ribs; sacrum). Recurrence occurred in 8 of the 14 patients with SNUC. The recurrences were local in five patients (frontal lobe; brain, clivus, and frontal bone; nasal vestibule; nasal cavity; and skull/scalp) and distant in three patients (lung; spine and pelvis; liver), two of whom also had local recurrence.

Kadish staging was as follows: 2 patients had stage A tumors; 7, stage B; and 17, stage C. One patient (with Kadish stage B tumor) was excluded from the survival analysis because she died of pulmonary embolism in the immediate postoperative period. Of the 8 patients with Kadish stage A or B tumors, 6 (75%) remained disease free for more than 2 years, compared with only 5 (29%) of the 17 patients with Kadish stage C tumors ( $P = .04$ , Fisher's exact test).

Hyams grading was as follows: 3 patients had grade I tumors; 4, grade II; 4, grade III; and 11, grade IV (Figs. 1 and 2). The same patient mentioned above who died of pulmonary embolism had a Hyams grade I tumor and was excluded from the survival analysis. Of the 6 evaluable patients with grade I or II tumors, 4 (67%) remained alive for more than 2 years, compared with only 4 (27%) of the 15 patients with grade III or IV tumors ( $P = .11$ , Fisher's exact test). Three patients with Kadish stage C tumors (2 esthesioneuroblastomas and 1 SNUC) survived more than 5 years. Two patients with Hyams grade IV tumors (1 esthesioneuroblastoma and 1 SNUC) also survived more than 5 years.

Of the 11 evaluable patients with esthesioneuroblastoma, 9 (82%) were alive at 2 years and 6 (55%) were alive at 5 years. Of the 14 evaluable patients with SNUC, 6 (42%) were alive at 2 years and 2 (14%) were alive at 5

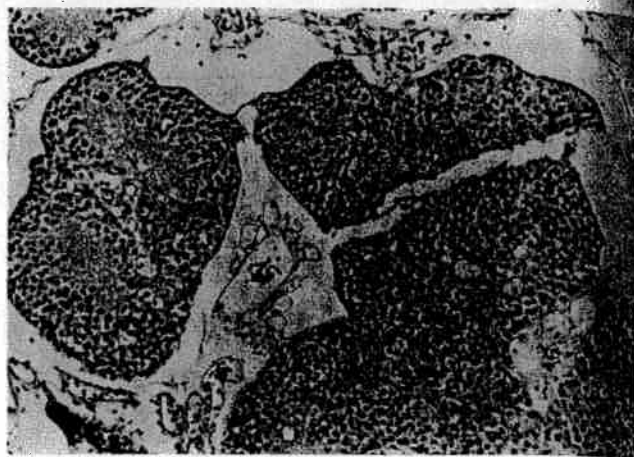


Fig. 1. Esthesioneuroblastoma demonstrating lobular architecture, minimal pleomorphism, absent mitotic activity, and prominent neurofibrillary matrix consistent with Hyams grade I tumor (H&E stain, original magnification  $\times 50$ ).

years. The Kaplan-Meier survival for the 25 evaluable patients was 57.3% at 2 years and 38.2% at 5 years. The Kaplan-Meier survival for the 11 patients with esthesioneuroblastoma (Fig. 3) was 71.6% at 2 years, and for the 14 SNUC patients, it was 45.1% at 2 years. Owing to the limited number of patients, 5-year survival could not be separately calculated for these groups. The survival for the SNUC patients was poorer, but this was not statistically significant.

## DISCUSSION

No prognostic system is uniformly accepted for the evaluation of esthesioneuroblastomas or SNUC. The early-stage and low-grade esthesioneuroblastomas have been reported to respond favorably to craniofacial resection followed by irradiation.<sup>4,7,8,11-13</sup> The advanced-stage and high-grade esthesioneuroblastomas and SNUC tumors generally respond poorly.<sup>3,4,7,8,11</sup> Our data demonstrate that patients with advanced Kadish stage or advanced Hyams grade tumors have a poorer chance of cure

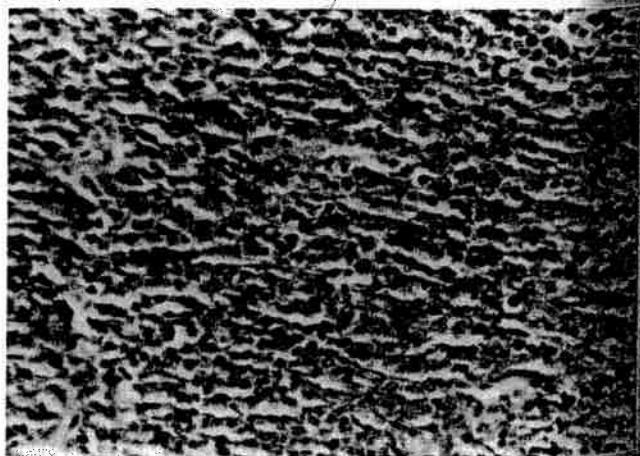


Fig. 2. Sinonasal undifferentiated carcinoma (SNUC) demonstrating solid undifferentiated growth, absence of neurofibrillary matrix, and moderate pleomorphism (H&E stain, original magnification  $\times 100$ ).

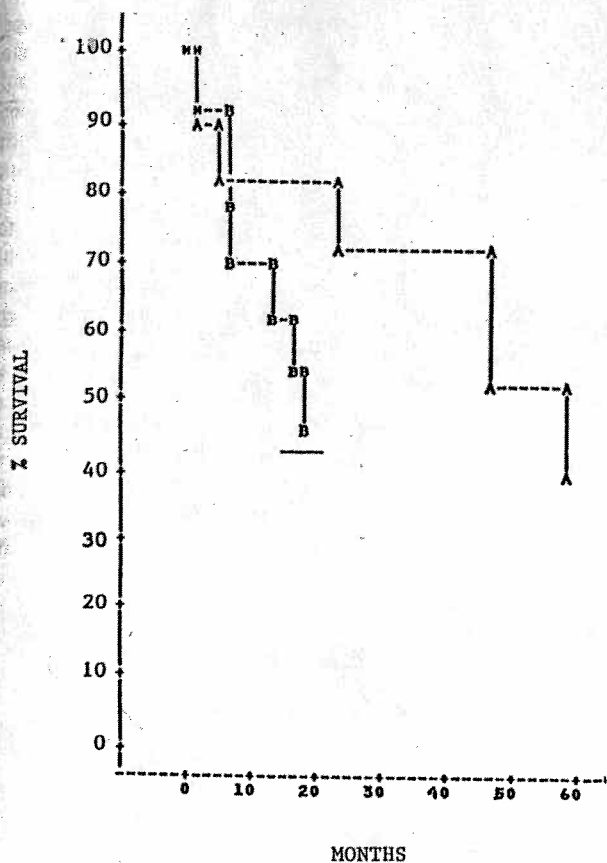


Fig. 3. Kaplan-Meier survival curves for patients with esthesioneuroblastoma (curve A) and SNUC (curve B).

even with aggressive therapy. Patients with Hyams grade III or IV tumors, whether classified as esthesioneuroblastoma or SNUC, have a poorer outcome than patients with well-differentiated esthesioneuroblastomas. However, we did find individual patients with advanced Kadish stage and Hyams grade who survived.

Our review, unlike others in the literature, concentrates on both Hyams and Kadish systems in regard to their utility in providing prognostic information for these tumor types. Other series, such as the University of Virginia series, reported survival for esthesioneuroblastoma as high as 80% at 8 years. However, their series classified all grade IV esthesioneuroblastomas as SNUC, and 80% of their tumors were Hyams grade I or II<sup>8</sup> compared with only 28% of tumors in our series. They did not advocate histological grading, but preferred the Kadish staging system.<sup>8</sup> Morita et al.<sup>4</sup> reported on 49 patients with esthesioneuroblastoma and found that the Hyams system correlated with clinical outcome. Other authors have found that the Hyams system is indicative of survival and that it may predict the utility of chemotherapy.<sup>5,14</sup> Clinical staging systems for esthesioneuroblastoma have been advocated by other authors,<sup>11,15</sup> but Kadish's system is most widely known.<sup>6</sup> In contrast to these other reports, Koka et al.<sup>16</sup> found only the presence of cervical metastases to be a prognostic factor.

Our series, although limited by small numbers of patients, demonstrates that both clinical staging and histolog-

ical grading provide useful prognostic information. Judging from our data, the use of aggressive therapy should not be denied to patients with clinically or histologically advanced esthesioneuroblastoma or SNUC tumors, because long-term survival is, at least, a possibility in these patients. Therefore the Kadish and Hyams staging systems can be useful in counseling patients with esthesioneuroblastoma or SNUC before embarking on major craniofacial surgery with its accompanying morbidity and mortality.

## CONCLUSION

Both the Kadish staging system and the Hyams grading system can be used independently to predict outcome. More advanced Kadish stage and higher Hyams grade predicted poorer survival, but there were patients in these categories who had long-term survival and aggressive therapy is warranted in selected cases.

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