Head and Neck Pathol (2015) 9:51–59
DOI 10.1007/s12105-014-0547-3

ORIGINAL PAPER

Prognostic Utility of Hyams Histological Grading and Kadish-Morita Staging Systems for Esthesioneuroblastoma Outcomes

Diana Bell · Rami Saade · Dianna Roberts · Thomas J. Ow · Michael Kupferman · Franco DeMonte · Ehab Y. Hanna

Received: 10 March 2014 / Accepted: 28 April 2014 / Published online: 8 May 2014
© Springer Science+Business Media New York 2014

Abstract Esthesioneuroblastoma (ENB) is derived from the specialized olfactory neuroepithelium. Hyams grading and Kadish staging have been used to prognosticate and to guide treatment decisions. In this study, we sought to validate the prognostic utility of these systems in a large ENB cohort. We retrospectively analyzed the records of patients with ENB who had been evaluated and treated at our institution. The association of grade and stage with prognostic outcome was assessed; the Kaplan–Meier estimator was used to generate 5-year OS and DFS curves. Out of 124 cases we identified, 121 were assessed for grading and 109 for staging. Review of the tissue samples revealed that 62 % of tumors were low grade (I/II) and 21 % were high grade (III/IV); 17 % of tumors were metastasis. The OS rate was 75 % at 5 years. The DFS was 60 % at 5 years. The OS was significantly worse for metastatic ENB (low-grade ENB vs metastatic ENB $p = 0.01598$); the DFS was significantly worse for high grade versus low grade ENB. Of the 109 cases that had been staged, 16 % were stage A, 33 % stage B, 43 % stage C, and 8 % stage D. In the A, B, and C groups, there were no significant differences between recurrence, distant metastasis, or 5-year survival rates. Statistical significance was not reached with the T, N, M and overall staging system. Age cutoff of 65 years reliably predicted OS. High grade of ENB was significantly associated with poor outcome, while advanced stage was not associated with poor outcome in this large cohort. Grading should certainly be considered in prognostication and treatment decisions for ENB.

Keywords Esthesioneuroblastoma · Hyams · Kadish · Morita

D. Bell (✉)
Departments of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: diana.bell@mdanderson.org

R. Saade · D. Roberts · M. Kupferman · F. DeMonte · E. Y. Hanna (✉)
Departments of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
e-mail: eyhanna@mdanderson.org

T. J. Ow
Department of Head and Neck Surgery, Montefiore Medical Center, New York City, NY, USA

Introduction

Esthesioneuroblastoma (ENB) is thought to arise from olfactory neuroepithelium, which originates at the olfactory placodes and in adults is replaced partially by respiratory mucosa. First described by Berger, Luc, and Richard in 1924, ENB has been characterized as a rare malignant neoplasm of the sinonasal cavity that arises in the superior portion of the nasal vault [1–4]. A variety of nomenclature has been used to describe this tumor (esthesioneuroblastoma, esthesioneuroepithelioma, esthesioneurocytoma, olfactory neuroblastoma (ON), and neuroendocrine carcinoma [4, 5]); the accepted terms at this time are esthesioneuroblastoma and olfactory neuroblastoma. Phenotypically, ENB is intermediate between that of a pure neural neoplasm (e.g., neuroblastoma and paraganglioma) and a neuroendocrine epithelial tumor (e.g., carcinoid, neuroendocrine carcinoma, small cell carcinoma) [5]. Due to variation in healthcare practices, resources, and departmental structure of surgical and pathology practices worldwide, currently ENB may be diagnosed individually or jointly by a general surgical pathologist, a head and neck pathologist, or by a neuropathologist each of whom might use slightly different terminology, as illustrated by the respective

ENB descriptions in the two corresponding WHO tumor classifications [2, 4, 5].

The olfactory epithelium is unique in the human nervous system in that it is capable of regeneration. The histologic organization of the olfactory organ reflects this ability. Several cell types are present in the olfactory epithelium: mature olfactory neuroepithelial cells, a basal layer of stem cells that repopulate the differentiated epithelium, sustentacular supporting cells, and flat cells forming the ducts of Bowman in the olfactory lamina propria [6–8]. These cell types are closely related and seem to be at least partly generated from a common progenitor cell during recovery after epithelial injury. The anatomic distribution of ENB is confined to the cribriform plate, the superior turbinate, and the superior third of the nasal septum. Rare cases of "ectopic" ENB have been reported for the nasopharynx, maxillary sinus, ethmoid sinus, and inferior meatus of nasal cavity entirely intracranial or in the sella turcica. ENB with no involvement of the cribriform plate should be a diagnosis of exclusion for ENB [2]. The differential diagnosis is broad: ENB can be confused histologically with several other "small blue round cell tumors" of the nasal cavity and paranasal sinuses [1, 2, 9]. Tumors commonly confused with ENB include sinonasal undifferentiated carcinoma, sinonasal neuroendocrine carcinoma, small cell carcinoma, pituitary adenoma, melanoma, lymphoma, and rhabdomyosarcoma. Therefore, thorough pathologic review and ancillary studies are essential to differentiating between these tumor types and properly diagnosing ENB.

Several factors make the characterization and treatment of ENB challenging. First the tumor is very rare, accounting for approximately 2 % of all malignant sinonasal tumors. Second, the tumor can be difficult to differentiate from several other neoplasms. Third, ENB itself can have variable biological activity, ranging from relatively indolent to both locally aggressive and metastatic.

The only histological grading system available for ENB was proposed by Hyams in 1988 on the basis of the Armed Forces Institute of Pathology experience [9]. This system categorizes each case of ENB into one of four grades, ranging from well differentiated (I) to least differentiated (IV), based on the tumor architecture, cellular pleomorphism, presence of neurofibrillary matrix and rosettes, mitotic activity, and presence of necrosis or calcifications.

The clinical staging system of ENBs was introduced by Kadish et al. [10]. In this study, however, it is uncertain the spectrum of histologic grading in the tumors, based on their descriptive criteria. This system was revised 17 years later by Morita et al. [11] to include a description of stage D tumors (consisting of cervical or distant metastases) and has been shown to be a good predictor of outcomes [12–15].

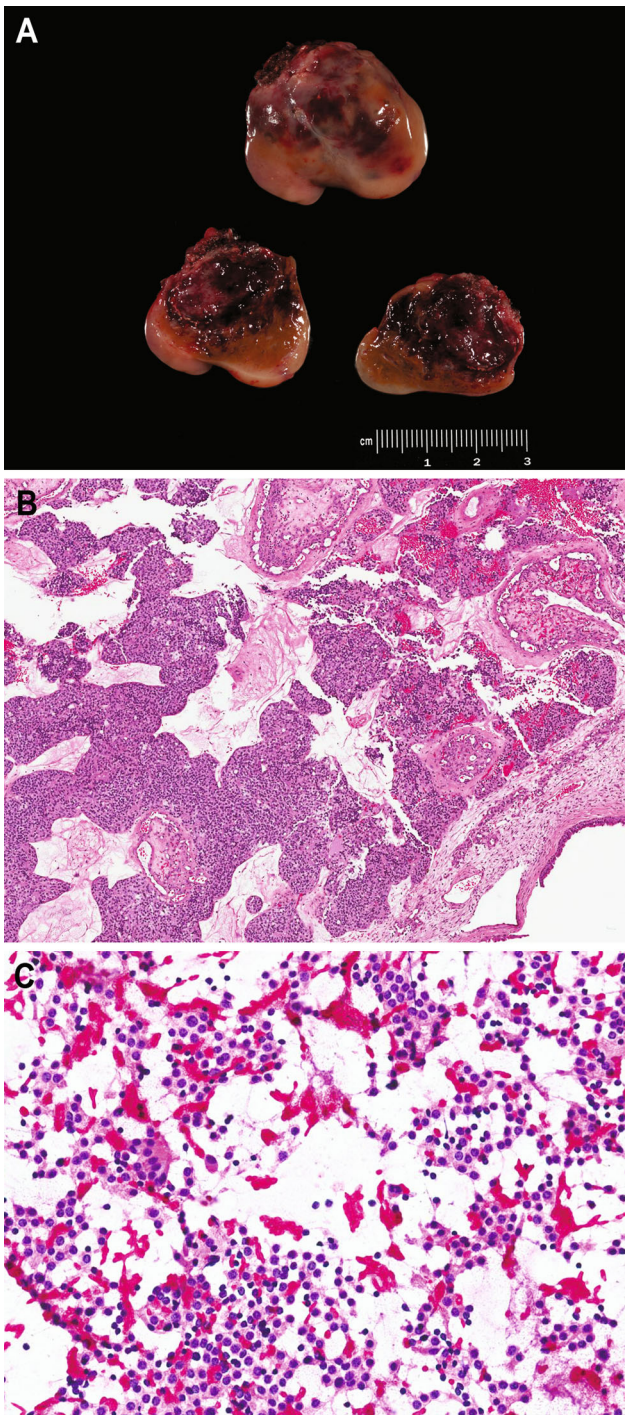


Fig. 1 Esthesioneuroblastoma classical case scenario. **a** gross appearance of polypoid *red-grey* mass, with hypervascular cut surface. **b** Frozen section diagnosis and **c** touch preparation of nasal cavity mass. Hematoxylin and eosin shows nests and lobules with fibrovascular stroma (**b**) consisting of uniform small cells containing scant cytoplasm and round to ovoid nuclei with indistinct nuclear membranes, punctuate chromatin and indistinct nucleoli (**c**) (ENB low grade)

The optimal treatment of ENB is controversial. Surgery followed by radiotherapy is considered by most treatment centers as the gold standard for management. The usefulness of neoadjuvant or adjuvant chemotherapy remains unknown, and the relevance of regional lymph node dissection or radiotherapy is controversial. Both the

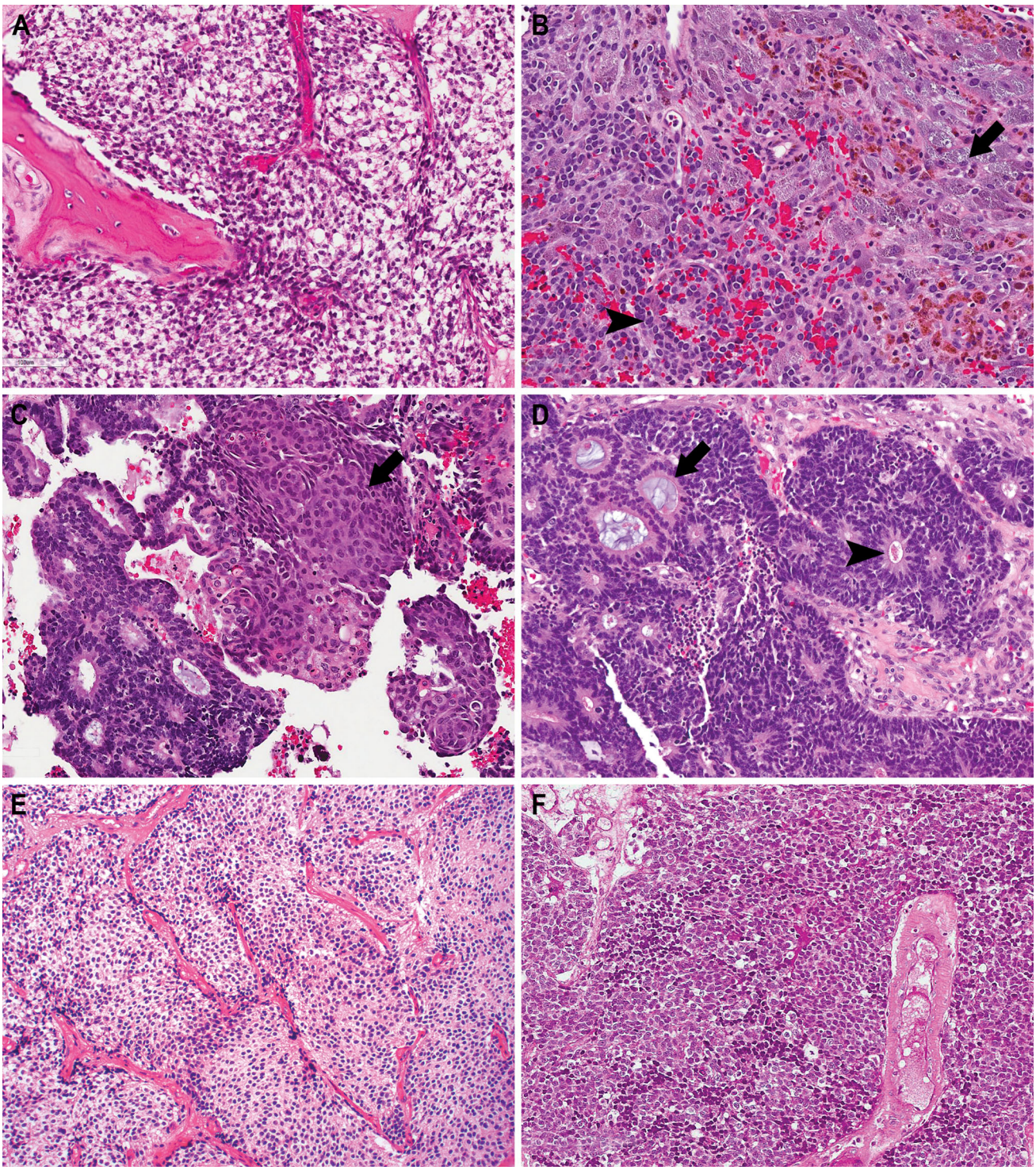


Fig. 2 Esthesioneuroblastoma uncommon findings. **a** Clear cell. **b** Melanin containing cells (*arrow*) and conventional small *blue* cells of esthesioneuroblastoma (*arrow-head*). **c**, **d** Divergent differentiation with glandular and squamous components (**c** *arrow* on squamous component; **d** *arrow* on glandular component, *arrowhead* on true rosette). **f** High grade ENB with *solid* pattern and minimal fibrillary background, in contrast to **e**. Low grade ENB (Hyams 1) with increased neurofibrillary matrix (identical to central neurocytoma)

Hyams grading and Kadish staging systems have been used to guide treatment decisions, including the appropriate use of neoadjuvant or adjuvant therapies. This has resulted in conflicting results between institutional case series and thus to different treatment recommendations.

In our retrospective study, we aimed to validate the prognostic ability of these grading and staging systems with a large cohort of ENB patients at our institution.

Materials and Methods

Patient Population and Data Collection

This retrospective single-institution study was approved by the Institutional Review Board. All medical reports of patients treated for or diagnosed with ENB at the institution between January 1990 and June 2013 were reviewed for clinical data: age, sex, risk factors, tumor stage, surgical management, post-operative treatment (radiotherapy including fields, and chemotherapy including regimens), recurrence, metastasis, and survival data. Cases with missing clinical data or unavailable material for histopathological reassessment were excluded from this study.

Histopathological Evaluation

The available hematoxylin- and eosin-stained slides of the patients in our cohort were reviewed by a dedicated head and neck pathologist (DB) expert in sinonasal neoplasia who was unaware of the clinical outcome, and the lesions were scored according to the Hyams grading system. This system is neither binary (+ or −) nor quantitative. The ENBs were classified using a mixed grading system that took into account the most common Hyams features. Occasional cases may show features that fall into both low-grade and high-grade categories. Grade III/IV was assigned to tumors morphologically recognizable as ENB, which had some but not all the criteria required to be classified as grade IV and could not be classified as pure grade III. The same algorithm was used for grade II/III. The presence of cellular pleomorphism, necrosis, and brisk mitotic activity override the presence of nested architecture and neurofibrillary matrix or rosettes. Because it is easier to use and generates similar results, we used a 2-tiered ENB grading system: low grade (I/II) (Fig. 1) and high grade (III/IV) (Fig. 2). Immunohistochemical analysis was performed, with a screening panel that included keratin cocktail, synaptophysin, S100, melanoma cocktail, and desmin, on all cases (either diagnostic biopsy or resection) in order to establish/confirm the ENB diagnosis.

Table 1 Characteristics, treatment, and margin outcome of 124 ENB patients from a single institution

Variable	%
Sex	
Male	61
Female	39
Self-reported smoking status	
Former smoker	28
Current smoker	14
Never smoker	56
Treatment modality	
Surgery	18
Surgery + chemotherapy	3
Surgery + radiotherapy	46
Surgery + chemotherapy + radiotherapy	24
Chemo + XRT	6
Chemotherapy	3
Tumor margins	
Unknown status	23.3
Negative	56
Positive (Gross/Macroscopic)	11.7
Positive (Microscopic)	9
Tumor stage	
T4	52
T3	16
Tx	18
T1/T2	14
Lymph node involvement	
N+	8 %
N2c (4 patients)	
N2b (4 patients)	
N1 (1 patient)	
N0	92 %

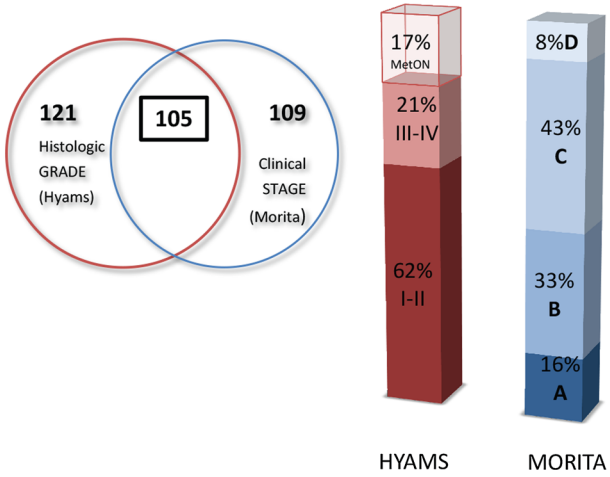
Statistical Analysis

Descriptive statistics for scaled values and frequencies of study patients within the categories for each of the parameters of interest were enumerated with the assistance of commercial statistical software. Curves describing overall and disease-free survival of patients were generated by the Kaplan-Meier product limit method. The statistical significance of differences between the actuarial curves was tested by the log rank test. Follow-up time was the time from first appointment at the University of Texas M. D. Anderson Cancer Center for the primary tumor of concern until the date of last contact or death for survival measurements. For disease-free survival plots, the starting point was the end of treatment for the original disease and the endpoint

Fig. 3 Patient characteristics (**a**), treatments (**b**), and tumor features (**c**) Abbreviations for Fig. 3: *XRT* radiation therapy, *surg* surgery, *chemo* chemotherapy, *CFR* craniofacial, *MDA* MD Anderson

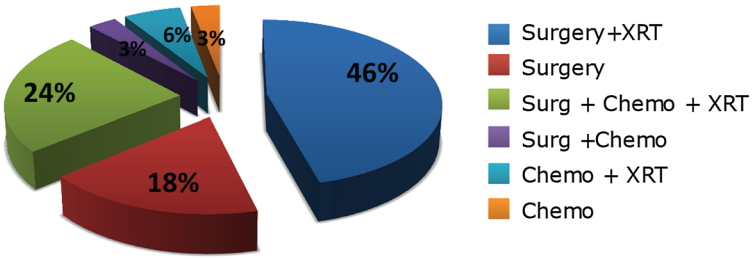
A **Patient Demographics & Tumor Characteristics**

Patient Characteristics	
Total	124
Age at Dx	
Mean	50.4 y
Median	52.4 y
Range	3.0 - 82.2 y
<65y	90 (79%)
>65y	24 (21%)
Gender	
Male	76 (61%)
Female	48 (39%)
Race/Ethnicity	
White	99 (80%)
Black	5 (4%)
Hispanic	14 (11%)
Asian	6 (5%)
Smoking	
Current	14%
Former	28%
Never	58%



B

- 56% definitive treatment at MDA
- 44% Seen at MDA after initial treatment



- Surgeries: 54% MDA vs. 46% Elsewhere

Open/Assisted CFR (68%)
Endoscopic: definitive (24%), not definitive (8%)

C

Patterns of recurrence

Mean follow up time 63 month (5years)

Pattern of Recurrence	Nb of patients	%
YES	50	42%
NO	70	58%
Site of 1st Recurrence		
Local	24	46%
Regional	17	32%
Distant	12	22%

Distant Metastasis	Nb of patients	%
YES	19	17%
NO	92	83%
Sites of DM		
Brain /Leptomeningeal	4	
Skull / Dura	2	
Spine / Bone	5	
Breast	1	
Lung	1	
Liver	1	
	1	

was first recurrence or death or last contact. These statistical tests were performed with the assistance of the Statistical (StatSoft, Inc., Tulsa, OK) statistical software application. Statistical results were considered when $p < 0.05$.

Results

a. Patient characteristics, treatments, and tumor features are summarized in Table 1 and Fig. 3.
b. Tumor histopathologic features

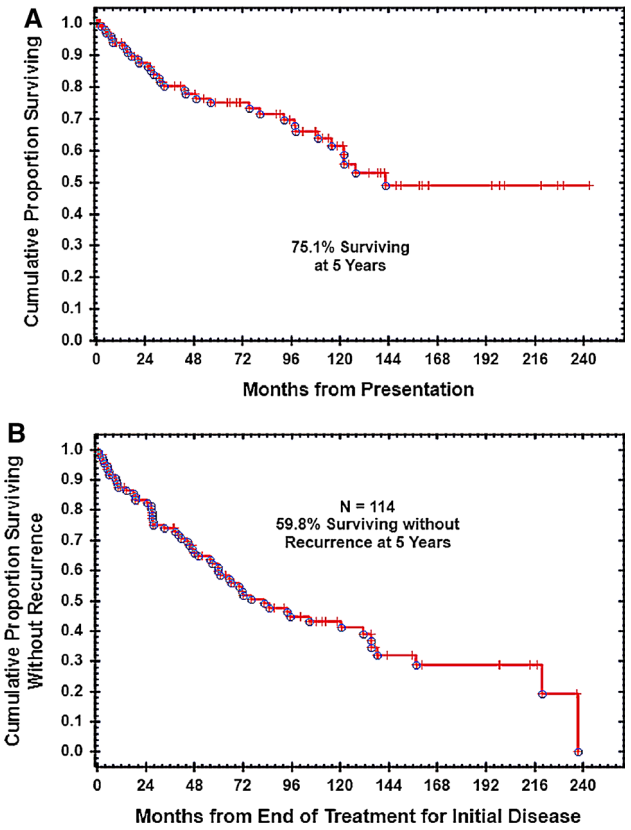


Fig. 4 The 5 years overall survival (**a**) and disease free survival (**b**)

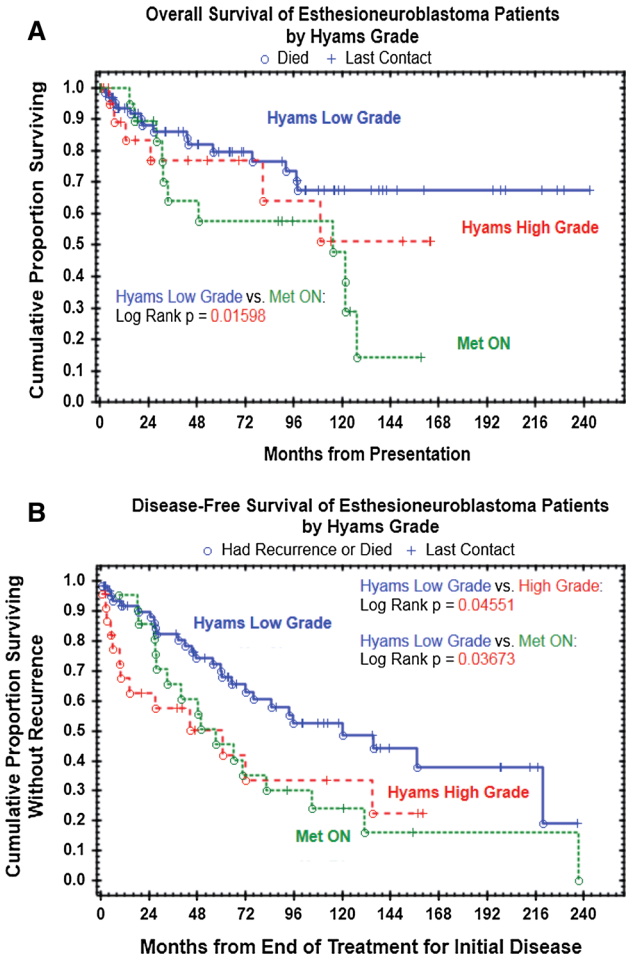


Fig. 5 Kaplan–Meier analysis revealed that the overall survival was significantly worse for metastatic ENB (**a**); the disease free survival was significantly worse for high grade versus low grade ENB (**b**)

Out of 124 ENB patients, 121 had slides available for histological assessment. Upon review of patients' slides, our pathologist graded 62 % as low grade (I/II) and 21 % as high grade (III/IV). The remainder of the patients had presented with cervical lymph node metastasis or with primary tumor resected elsewhere, or slides were not available for pathologic grading.

c. Tumor stages

Of the same 124 ENB patients, 109 tumors had been staged according to the Kadish-Morita system and categorized 16 % as stage A, 33 % as stage B, 48 % as stage C, and 3 % as stage D.

d. Association between tumor grade and prognosis, treatment, and outcomes

The 5 and 10 years overall survival was 75 and 55 % respectively, while the disease free survival was 60 and 40 % respectively (Fig. 4a, b). Distant metastasis was not significantly associated with histological grade (9 and 7 % in low-grade and high-grade tumors, respectively). Recurrence was less common in low-grade ENB than in high-grade ENB (23 vs. 12.5 %). Kaplan–Meier analysis revealed that the overall survival was significantly worse for metastatic ENB (low-grade ENB vs metastatic ENB $p = 0.01598$) (Fig. 5a); the disease free survival was significantly worse for high grade versus low grade ENB (low-grade vs high-grade ENB $p = 0.04551$; low-grade ENB vs metastatic ENB $p = 0.03673$) (Fig. 5b).

e. Association between tumor stage and prognosis, treatment, and outcomes

In the A, B, C and D groups, there were no significant differences between recurrence, distant metastasis, or 5-year survival rates (Fig. 6). Statistical significance was neither reached with T, N, M or overall staging system. Age cutoff of 65 years reliably predicted OS ($p = 0.03944$) (Fig. 7).

Discussion

The diagnosis and management of ENB have improved significantly in the last three decades, yet several important

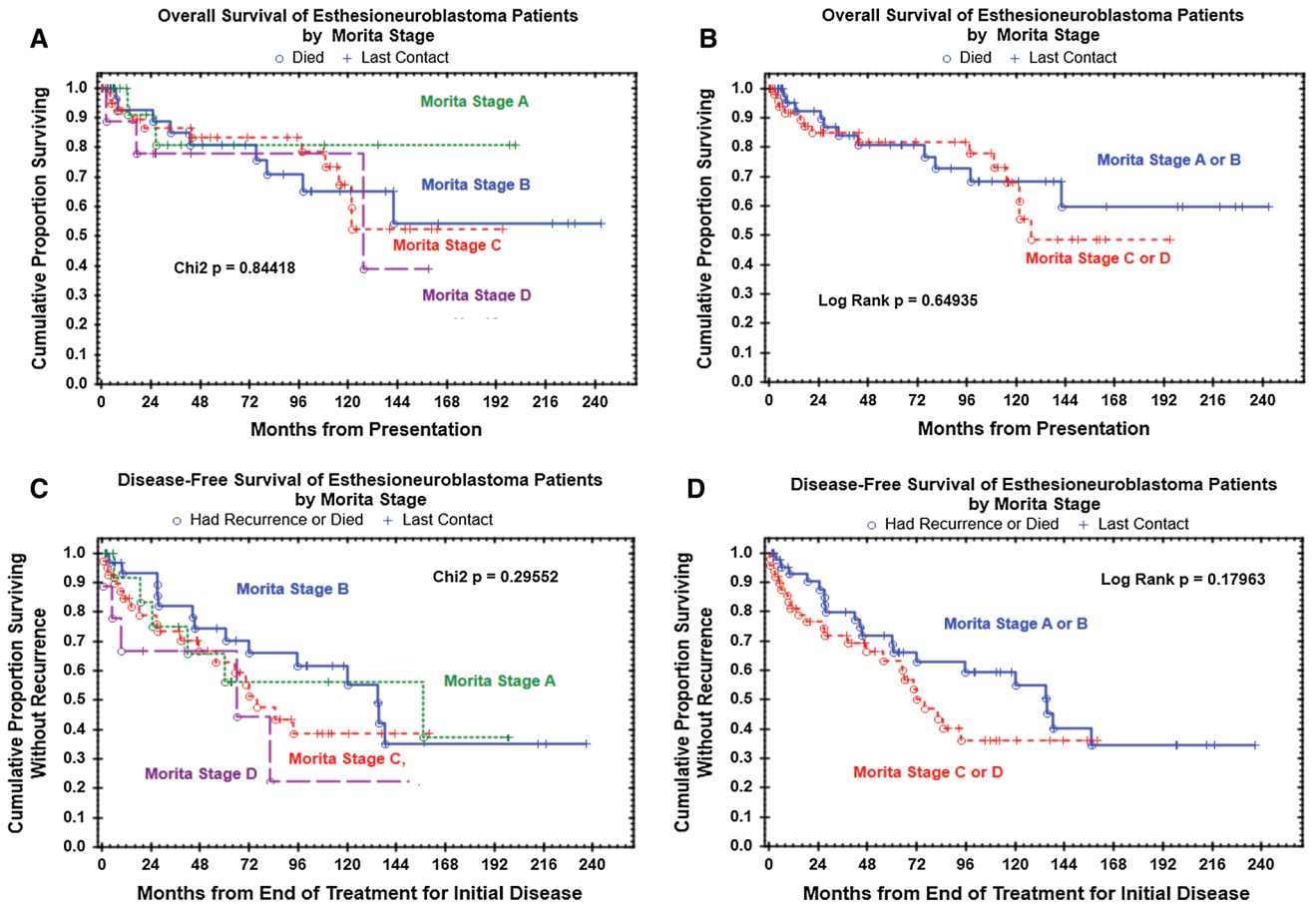


Fig. 6 In the **a**, **b**, **c** and **d** groups, there were no significant differences between recurrence, distant metastasis, or 5-year survival rates

questions remain unanswered. As the recurrence patterns of this disease are better described with long-term studies using large patient sets, it will become more clear which staging and grading systems are most accurate and useful for guiding treatment and for prognostication [4].

Both the Hyams grading system and the Kadish staging system have been used to provide a prognosis for ENB patients and to help guide treatment decisions, including the appropriate use of neoadjuvant or adjuvant therapies. The Hyams grading scheme captures the spectrum of ENB maturation. Several groups have asserted that grade III and more predominantly grade IV ENBs are in fact sinonasal undifferentiated carcinomas (SNUCs). The main differential diagnosis is between high-grade ENB and SNUC, which has clinical relevance because SNUC is considered to have a much worse prognosis than ENB. We have validated the findings from our systematic review with a detailed dataset collected retrospectively from our institution. To our knowledge, the current study is the largest cohort of ENB patients to date from a single institution that has been reported in the literature, and the largest series for which the Hyam's grading scale has been applied to evaluate the association with patient outcome.

In an analysis of survival and prognostic factors, Jethanamest et al. [16] applied the modified Kadish staging system to 261 cases of ENB from the SEER database. Cox regression analysis results showed that the staging system was a significant predictor of disease-specific survival [16]. The influence of the Hyams grading system is controversial and yet to be fully understood. A recent large study from the Mayo Clinic concluded that the extent of involvement at presentation (Kadish stage and lymph node metastasis) and a higher Hyams grade were the two factors that appeared to have the greatest impact on prognosis [17]. That retrospective single-institution study included 109 patients, 87 of whom had histological information available for analysis. Dulguerov reported in 1992 a 5-year survival rate of 74 % [14]. In the Mayo Clinic review, Hyams grades were as follows: grade I 6 %, grade II 48 %, grade III 37 %, grade IV 9 %; for multivariate analysis, grade I and IV were included with grade II and III-low and high grade respectively. The Mayo results for low-grade tumors (54 %) are similar to those found at MDACC (62 %), however the Mayo series reported a higher number of high grade lesions (46 % Mayo compared to 21 % MDACC). The cohort at Mayo included 87 patients with available

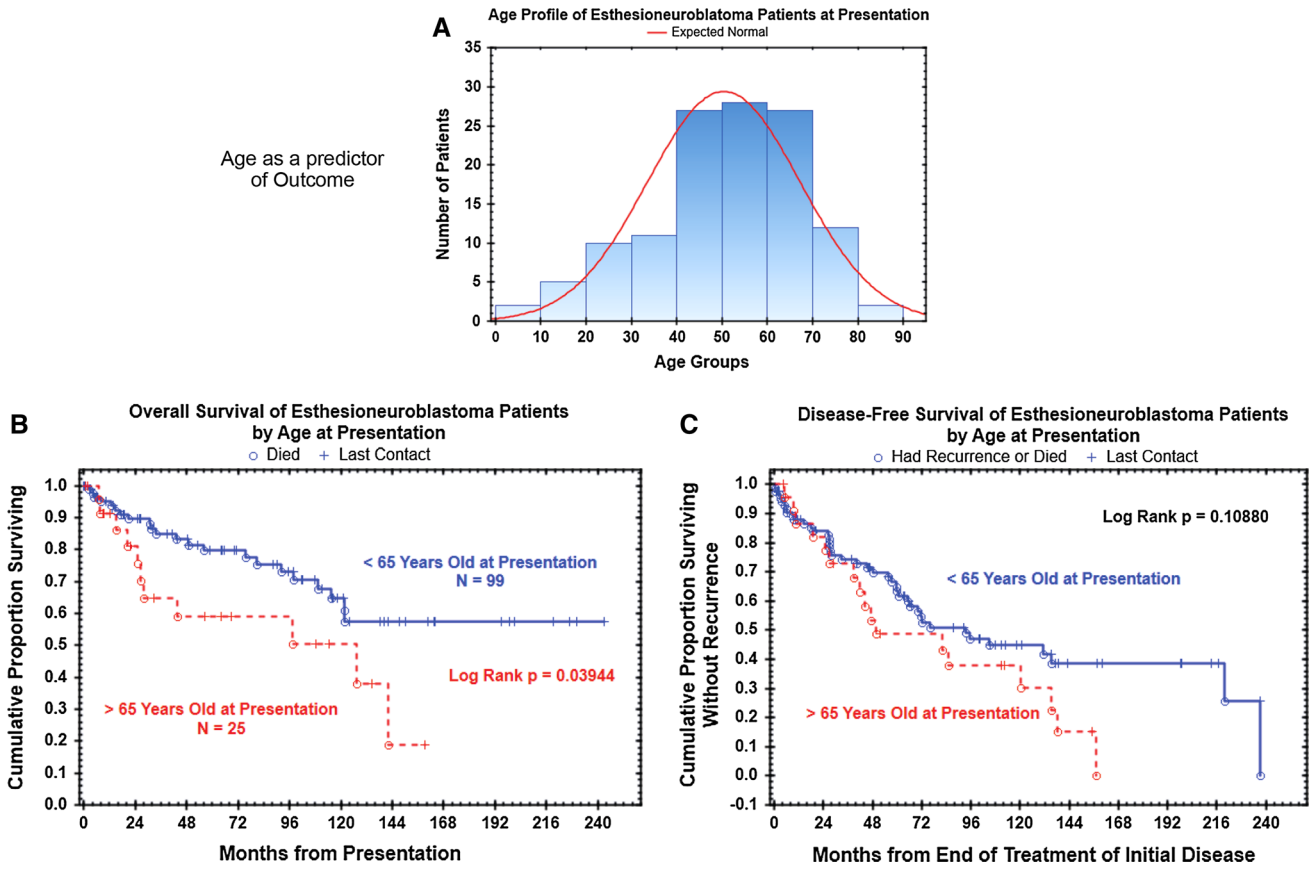


Fig. 7 Age cutoff of 65 years reliably predicted OS

pathology slides, versus 121 in MDACC study, however here 21 patients (17 %) presented with cervical lymph node metastasis, with primary tumor resected elsewhere and/or not available for pathologic grading. The Mayo series also reached statistical significance for Hyams low and high grade ($p = 0.04$, and Hyams 4 had a particularly poor outcome $p < 0.001$); this outcome was very close to MDACC's ($p = 0.004$). In our review, grade III/IV was assigned to tumors that were morphologically recognizable as ENB, which had some but not all the criteria required to be classified as grade IV and could not be classified as pure grade III. In the current study, cellular pleomorphism, necrosis, and brisk mitotic activity, override nested architecture, and the presence of neurofibrillary matrix or rosettes.

The Hyams grading scheme, which covered work predating the first description of SNUC by nearly 10 years, captures the spectrum of ENB maturation. Several groups have asserted that grade III and predominantly grade IV ENBs are in fact SNUCs [18–20]. Of note, the smear pattern of SNUC (i.e., hypercellularity, prominent necrosis, pyknosis, high nuclear:cytoplasmic ratio) mirrors closely the findings for a series of high-grade ENBs [18]. A 44-patient series from the Institut Gustave Roussy depicted low- and high-grade ENBs with distinct patterns at presentation and relapse: high-grade ENB was associated with T4 stage, frequent lymph node involvement, unresectability, and leptomeningeal metastasis, whereas low-grade ENB was associated with late locoregional recurrence) [21]. In the UCSF series of 20 ENB cases, Kaur et al. demonstrated that the Hyams criteria was the best way of predict prognosis and selecting patients for adjuvant therapy. In that series, the 5- and 10-year survival rates were 86 % for patients with low-grade ENB and 56 and 28 % for patients with high-grade ENB, respectively [22]. However, in their series all of these cases irrespective of histologic grade were high stage (stage C).

The variability of the results from this series highlight that a centralized pathology review would benefit our understanding of ENB. The published studies and the SEER case series based on tumor grade support a bias toward low-grade ENB, but there is also compelling literature demonstrating that low- and high-grade tumors are evenly distributed and that do not affect the outcome. Molecular and genetic evaluation should be added in the future to the diagnostic workup of tumors in order to refine

the ability to discriminate poorly differentiated/high-grade ENB from other high-grade undifferentiated neoplasms [23].

Conclusions and Remarks

Histological grading reached statistical significance, while there was no significance among Kadish-Morita stages in predicting outcome. Understanding of ENB tumor biology continues to evolve and will likely facilitate the development of improved treatment strategies for this disease. Increasingly sophisticated pathological assessments and the elucidation of molecular markers in ENB could transform the clinical management of these tumors. The identification of molecular abnormalities underlying ENB and those responsible for carcinogenesis is critical to the development of specific targeted therapies and the design of clinical trials. Because of the rarity of this entity, it is difficult for a single institution to accrue large numbers of patients. For this reason, multi-institutional and international collaboration will be necessary in collecting data prospectively and retrospectively and in reporting outcomes in a uniform manner using a common database.

Acknowledgments This study was supported in part by MDACC start-up funds (DB). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or National Institutes of Health.

Conflict of interest None.

References

1. Bell D, Hanna EY. Sinonasal undifferentiated carcinoma: morphological heterogeneity, diagnosis, management and biological markers. Expert Rev Anticancer Ther. 2013;13:285–96.
2. Faragalla H, Weinreb I. Olfactory neuroblastoma: a review and update. Adv Anat Pathol. 2009;16:322–31.
3. Klepin HD, McMullen KP, Lesser GJ. Esthesioneuroblastoma. Curr Treat Options Oncol. 2005;6:509–18.
4. Ow TJ, Bell D, Kupferman ME, Demonte F, Hanna EY. Esthesioneuroblastoma. Neurosurg Clin N Am. 2013;24:51–65.
5. Platek ME, Merzianu M, Mashtare TL, et al. Improved survival following surgery and radiation therapy for olfactory neuroblastoma: analysis of the SEER database. Radiat Oncol. 2011;6:41.
6. Franssen EH, de Bree FM, Verhaagen J. Olfactory ensheathing glia: their contribution to primary olfactory nervous system regeneration and their regenerative potential following transplantation into the injured spinal cord. Brain Res Rev. 2007;56:236–58.
7. Holbrook EH, Wu E, Curry WT, Lin DT, Schwob JE. Immunohistochemical characterization of human olfactory tissue. The Laryngoscope. 2011;121:1687–701.
8. Uraih LC, Maronpot RR. Normal histology of the nasal cavity and application of special techniques. Environ Health Perspect. 1990;85:187–208.
9. Hyams VJ. Olfactory neuroblastoma (Case 6). In: Batsakis JG, Hyams VJ, Morales AR, editors. Special tumors of the head and neck. Chicago: ASCP Press; 1982. p. 24–9.
10. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer. 1976;37:1571–6.
11. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993; 32:706–714; discussion 714–705.
12. Bachar G, Goldstein DP, Shah M, et al. Esthesioneuroblastoma: the Princess Margaret Hospital experience. Head Neck. 2008;30:1607–14.
13. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol. 2001;2:683–90.
14. Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970–1990. The Laryngoscope. 1992;102:843–9.
15. Zafereo ME, Fakhri S, Prayson R, et al. Esthesioneuroblastoma: 25-year experience at a single institution. Otolaryngol Head Neck Surg. 2008;138:452–8.
16. Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma—a population-based analysis of survival and prognostic factors. Arch Otolaryngol Head Neck Surg. 2007;133:276–80.
17. Van Gompel JJ, Giannini C, Olsen KD, et al. Long-term outcome of esthesioneuroblastoma: hyams grade predicts patient survival. J Neurol Surg B Skull Base. 2012;73:331–6.
18. Bellizzi AM, Bourne TD, Mills SE, Stelow EB. The cytologic features of sinonasal undifferentiated carcinoma and olfactory neuroblastoma. Am J Clin Pathol. 2008;129:367–76.
19. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. Adv Anat Pathol. 2005;12:134–43.
20. Iezzoni JC, Mills SE. "Undifferentiated" small round cell tumors of the sinonasal tract: differential diagnosis update. Am J Clin Pathol. 2005;124(Suppl):S110–21.
21. Malouf GG, Casiraghi O, Deutsch E, Guigay J, Temam S, Bourhis J. Low- and high-grade esthesioneuroblastomas display a distinct natural history and outcome. Eur J Cancer. 2013;49:1324–34.
22. Kaur G, Kane AJ, Sughrue ME, et al. The prognostic implications of Hyam's subtype for patients with Kadish stage C esthesioneuroblastoma. J Clin Neurosci. 2013;20:281–6.
23. Weiss GJ, Liang WS, Izatt T, et al. Paired tumor and normal whole genome sequencing of metastatic olfactory neuroblastoma. PLoS ONE. 2012;7:e37029.