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HEAD AND NECK CANCERS (E HANNA, SECTION EDITOR)

Prognosis and Biology in Esthesioneuroblastoma: the Emerging Role of Hyams Grading System

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Abstract Esthesioneuroblastoma is a sinonasal tumor with distinct clinicopathologic features, multiple facets, and a spectrum of behavior. Characterization of this disease is challenging, and clinically, several staging systems have been used with no consensus on a single scheme. Recently, the Hyams histological grading system has emerged as a promising prognostication tool that offers an added value to stage. This review addresses prognosis and biology in esthesioneuroblastoma. More specifically, we sought to present a critical appraisal on the value of each of these stratification systems, stage vs. grade, in identifying risk groups and guiding management.

Keywords Esthesioneuroblastoma · Olfactory Neuroblastoma · Hyams · Kadish · Morita · Stage · Grade · Prognosis · Outcome

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Introduction

Esthesioneuroblastoma (ENB) is a rare malignant neoplasm of the sinonasal tract, first described by Berger, Luc, and Richard in 1924 [1]. This superior nasal vault tumor is thought to derive from the specialized olfactory neuroepithelium. The exact location and cell type it arises from has yet to be defined, and over the last decades, this same pathology has been attributed several names: olfactory neuroblastoma, neuroendocrine carcinoma, esthesioneuroepithelioma, and esthesioneurocytoma, among others. However, the common ground is a neural crest/immature olfactory neuron origin, suggested from the typical neural filaments present in tumor cells and from molecular analyses [2]. The most commonly adopted and accepted nomenclatures remain esthesioneuroblastoma and olfactory neuroblastoma.

Sinonasal tumors are relatively rare and represent a diverse and heterogenous group of malignancies. ENB accounts for only 3 % of all sinonasal tumors [3]. Although a bimodal age presentation has been entertained initially, more recent reports rather support an even distribution across all ages with peaks in the fifth and sixth decade [4, 5]. Clinically, ENB often has a subtle presentation mimicking benign inflammatory/infectious disease and delay in diagnosis is not uncommon. Nasal obstruction and epistaxis are typical early manifestations; however, other more specific symptoms can occur depending on the location and extent of the tumor. A thorough physical exam and flexible fiberoptic endoscopic evaluation, complemented with both contrast-enhanced CT scan and MR imaging, are key in the diagnostic workup. Histologically, well-differentiated ENB forms nests or sheets of cells in a neurofibrillary stroma. Nuclei are small, round to ovoid with punctuate "salt and pepper" chromatin. The glandular architecture with true lumen rosette (Flexner-Wintersteiner) or pseudorosette (Homer-Wright) formations is characteristic. The typical immunohistochemical profile for

ENB demonstrates diffuse staining for neuron-specific enolase, chromogranin, and synaptophysin as well as variable S-100 positivity.

Challenges in the Characterization of ENB

ENB falls under the "small round blue cell" category with a broad and intricate differential diagnosis, including sinonasal undifferentiated carcinoma (SNUC), sinonasal neuroendocrine carcinoma (NEC), small cell carcinoma (SmCC), melanoma, pituitary adenoma, rhabdomyosarcoma, and lymphoma [6]. In their report on misdiagnosis of ENB, Cohen et al. [7] highlight the common confusion of other pathologies with ENB. Out of 12 patients referred to a tertiary center with a diagnosis of ENB, only 2 were actually confirmed to be ENB after review of their specimens by dedicated head and neck pathologists. The remaining patients required significant alteration in their initially proposed treatment plan. In fact, in the landmark publication by Rosenthal et al. [8] on the outcome and prognosis of sinonasal malignancies with neuroendocrine differentiation, two distinct groups were observed: ENB and non-ENB (SNUC, NEC, and SmCC). Significantly higher overall survival, loco-regional, and distant control rates were seen in the ENB group as opposed to the non-ENB group. The emphasis is thus on accurate diagnosis, ideally by specialized head and neck pathologists to provide adequate treatment and achieve better outcomes.

Besides their rarity and complex differential diagnosis, perhaps, one of the most challenging aspect in the characterization and management of ENB is the broad spectrum of biology individual tumors can exhibit, from indolent disease to more aggressive and metastatic behavior.

Therefore, optimal management of ENB really lies on a more accurate patient stratification to identify risk groups and individualize care. Broadly, two stratification systems are in use: staging and grading. Both have been adopted to guide treatment planning. This has led to some debatable recommendations by different institutional series. With the exception of very early and limited disease, multimodality management offers the best chance for cure. Surgery followed by radiotherapy is considered by most expert centers the gold standard [9]. However, in a more advanced disease, the impact of neoadjuvant and adjuvant chemotherapy remains unknown and the relevance of regional lymph node dissection or inclusion in irradiation fields is controversial. What is at stake in establishing the prognostic value of staging vs. grading in ENB is to better predict outcomes and therefore to better address the appropriate use of these adjuvant or neoadjuvant therapies.

Utility of the Staging Systems

Several staging systems have been proposed and no single one has become universally accepted. Kadish staging was the first classification system for ENB. Although it was initially described based on 17 patients only, it remains the most popular and simplified go-to staging system [10]. Its main limitation resides in the fact that this system only assesses local disease extent: Kadish A for tumors limited to the nasal cavity only, Kadish B for involvement of the paranasal sinuses, and Kadish C for extension outside the paranasal sinuses. Dulguerov [11] and Biller [12] then proposed more detailed TNM-type staging systems. Dulgerov's classification differentiates between intracranial and/or orbital extension whereas Billers' separates resectable vs. non-resectable parenchymal brain disease. More importantly, both of these staging systems take into account regional neck node involvement and distant metastasis. Lymph node metastasis was in fact shown to be in itself a major determinant of prognosis and to be associated with poorer outcome. In the Princess Margaret report, Dulguerov classification correlated most closely to survival and recurrence [13]. Zafereo et al. [14] also demonstrated that the TNM-based systems (Dulgerov and Biller) in contrast to Kadish staging could reliably identify worse disease-free survival. Therefore, recognizing the poor prognostic implications of regional and distant disease, Morita proposed a more accurate and practical modification to the Kadish system [15]. Cervical lymphadenopathy and distant metastasis are incorporated as a fourth "D" category. In this scheme, Jethanamest et al. [5] in a SEER database review showed significant outcome differences among the four groups with a worse disease-free survival for the D category. Despite the efforts to better characterize ENB's clinical behavior, staging systems individually are far from ideal. While some have used them as predictors of outcome, they remain, for many, questionable and suboptimal tools of stratification.

The Added Value of the Grading System

Perhaps, one of the earliest reports that noted a possible role for histopathologic grading in predicting outcome was Dulguerov's meta-analysis in 2001 [16]. Although grading was not the main parameter of interest and was only identified in few studies, advanced grade tumors did demonstrate poorer outcome. In 2010, Kane et al. [17] published a meta-analysis that confirmed the prognostic value of modified Kadish staging, lymph node involvement, and age at diagnosis, as previously noted in the SEER database review. However, the authors further identified higher grade (by Hyams criteria) to predict poorer prognosis.

Therefore, beyond staging, the actual histologic grade of a tumor can give a great insight on its biology. The Hyams

grading system, proposed back in the late 80s by the American Forces Institute of Pathology [18], is a scheme that captures the spectrum of ENB maturation; from indolent disease to more aggressive behavior. A score from 1 to 4 is given based on the degree of expression of key adverse features: mitotic activity, nuclear pleomorphism, rosette formations, necrosis, disorganized architecture, and sparse fibrillary matrix (Fig. 1).

There are few inherent flaws to this stratification system. First, grading can be subjective with possibly some level of discordance among pathologists. Second, diagnoses based on aspirations and needle core biopsies can result in sampling errors; either missing the tumor or assessing only one lower-grade front. Third, histologic reading can pose difficulties in the interpretation of poorly differentiated tumors as they can mimic more aggressive non-ENB tumors. This is usually less of a problem in high-volume centers with specialized head and neck pathologists. However, in smaller institutions, where ENB cases present sporadically, even the most experienced pathologists might not have enough exposure to distinguish the subtle nuances.

Therefore, initial data supporting the value of this system for prognostication has been critically received. Currently, a building body of evidence is trending towards validation of grade as an essential tool in prognostication and management.

One of the recent reports that evaluated the prognostic value of Hyams grading in ENB came from the Mayo clinic group [19••]. They observed modified Kadish stage, lymph node metastasis, age, and higher Hyams grade to be significant prognosticators. Out of 109 ENB patients, 87 had available histology to review. Patients were grouped into low grade (Hyams I–II) and high grade (Hyams III–IV). Up to 46 % of reviewed specimens were noted to be high grade. The 5-year overall survival was 63 %, less than the 73 % rate observed by Dulgerov's report. Hyams grade in the Mayo series reached statistical significance for prognostication, and Hyams 4 had a particularly poor outcome. One possible caveat to this paper is the retrospective inclusion of patients from 1962 to 2009, with 35 % of them pathologically diagnosed before 1990, an era where SNUC was not yet fully recognized and first described in 1986 by Frierson et al. [20]. Because of the overlap in histologic patterns seen in high-grade ENB and SNUC, the concern is that some high-grade ENB might be confused with SNUC. This is significant since SNUC is a distinct pathology of worse prognosis and is managed differently.

This was followed by the UCSF report [21••]. In this 20-patient cohort, Kaur et al. studied patients with extensive disease (beyond the paranasal sinuses, Kadish C). The respective 5- and 10-year overall survival for low-grade ENB was 86 % in comparison to 56 and 28 % for high-grade ENB. The authors conclude that Hyams grade is complementary to stage and is the best tool to predict prognosis of advanced disease (Kadish C) and to select patients for adjuvant therapy.

The Institue Gustave Roussy also addressed the value of Hyams grading in ENB [22••]. In a review of 44 patients, Hyams grade was an independent predictor of overall survival, as was Dulgerov's T stage. The analysis revealed two distinct patterns of presentation and recurrence according to Hyams grade. The first group (Hyams III and IV) was associated with bulkier tumors (T4 stage), more cervical lymphadenopathy, frequent unresectable disease, and leptomeningeal metastasis. In contrast, low-grade tumors (Hyams I and II) typically formed late loco-regional recurrences.

The latest contribution to ENB literature is a large single institutional restrospective review from MDA [23••]. Out of 124 ENB cases identified, 121 were assessed for Hyams grading and 109 for modified Kadish staging. Histologically, 62 % of tumors were low grade (I/II), 21 % were high grade (III/IV), and 17 % were metastasis. Five-year OS and DFS rates of 75 and 60 % were achieved, respectively. Metastatic ENB had significantly worse OS and high-grade ENB had significantly worse DFS. Clinically, of the 109 cases that had been staged, 16 % were stage A, 33 % stage B, 43 % stage C, and 8 % stage D. The analysis revealed no statistically significant differences, for either modified Kadish stages or TNM stages, in terms of recurrence, distant metastasis, or 5-year survival rates. Briefly, in this large cohort on ENB, high grade was significantly associated with poor outcome, while advanced stage was not.

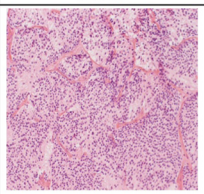
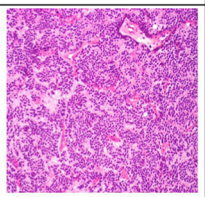
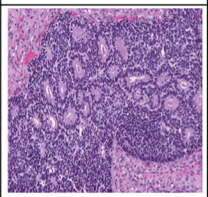
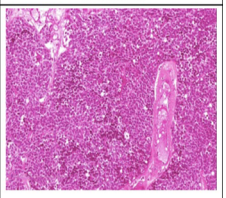
HYAM's	Grade 1	Grade 2	Grade 3	Grade 4
Architecture	Lobular	Lobular	Variable	Variable
Mitotic Activity	Absent	Present	Prominent	Marked
Nuclear Pleomorphism	Absent	Moderate	Prominent	Marked
Fibrillary Matrix	Prominent	Present	Minimal	Absent
Rosette	HW	HW	FW	FW
Necrosis	Absent	Absent	+/- Present	Common
Hematoxylin & Eosin				

Fig. 1 Key features and criteria for HYAMS grades I, II, III, and IV and their corresponding histopathologic H&E slides

Each of these four institutional reports has led us forward in defining the value and utility of Hyams grading. In summary, a high Hyams score (III/IV) is associated with more aggressive locoregional disease (IGR) and is a predictor of worse DFS (MDA). Practically, in clinically advanced disease, Hyams grading has a prognostic value and can guide selection for adjuvant treatment (UCSF). Whether the Hyams histopathologic grading is by itself a sufficient stratification tool and an independent predictor of overall survival (Mayo) has yet to be determined (Table 1).

In an effort to optimize the prognostic utility of the grading system, Gallager et al. [24] revisited the Hyams criteria and tried to identify additional histologic variables that could predict outcome. Twenty-seven ENB patients were retrospectively studied. The authors confirmed necrosis and mitosis to be significant predictors of OS and DFS, but not as individual parameters. Gland hyperplasia, a criterion not typically accounted for in the Hyams grading, was also found to be a positive prognostic variable. It was associated with longer overall and disease-free survival, but only in combination with absence of spindle features and necrosis. Essentially, the study calls for an update of Hyams histologic criteria to provide more valuable prognostic information in ENB.

Future Directions and Perspectives

An interesting study by Kim et al. [25] aimed at identifying ENB tumor markers of prognostic significance. Bcl-2 (anti-apoptotic and pro-angiogenic molecule) [26] immunoreactivity was noted in 65 % of specimens (15 out of 17 tumors). Although Bcl-2 was not a statistically significant predictor of survival ($p=0.06$), the authors did observe a direct trend towards better response to neoadjuvant chemotherapy in patients with diffuse Bcl-2 expression. Fukushima et al. [27] then demonstrated a strong correlation between Bcl-2 expression and higher Hyams grades. Of course, these studies are still at the investigational level and do not translate yet clinically. Efforts to decipher ENB tumor biology are underway and understanding the disease behavior continues to evolve. A major role for molecular markers is foreseen in improving prognostication and treatment strategies. Increasingly refined pathological diagnostic tools are also anticipated to impact the clinical management of ENB.

The ultimate goal is to identify key molecular alterations in ENB and to develop targeted therapies. ENB is a rare disease that requires multi-institutional and international collaboration. A centralized processing of ENB cases would offer the most favorable ground to accrue more patients and use a uniform database in collecting information and reporting outcomes.

Conclusion

Traditionally, several staging systems have been in use to stratify ENB patients into risk groups and to guide the management. However, no single clinical staging system has consistently shown to be a reliable predictor of outcome. More recently, histopathologic Hyams grading has proven to accurately characterize the tumor's biology and to be an independent predictor of locoregionally aggressive disease and worse DFS. The full breadth of the Hyams grading system in prognostication still has to be established. Nonetheless, it remains a valuable asset to consider when dealing with clinically advanced ENB and contemplating adjuvant therapy. The histopathologic grade of ENB offers an added value to clinical stage and should therefore complement it in decision-making.

Table 1 Summary on the four major institutional reviews addressing the value of Hyams grading in predicting outcome in Esthesioneuroblastoma

ENB studies addressing Hyams prognostic value	Study design	Total Nb of patients with ENB	Nb of patients with available Hyams grade	Patients with high-grade III–IV Hyams (%)	Predictors of outcome
Van Gompel et al. 2012 [19••] -Mayo-	Retrospective review 1960–2009	109	87	46	Modified Kadish, Hyams, LN metastasis, and age are predictors of OS
Kaur et al. 2013 [21••] -UCSF-	Retrospective review 1995–2009	20 (all are Kadish C)	20	56	Hyams is a predictor of PFS in Kadish C patients
Malouf et al. 2013 [22••] -IGR-	Retrospective review 1979–2009	44	31	58	Compared to low-grade tumors, high-grade ENB exhibit distinct patterns of presentation and worse DFS and OS
Bell et al. 2014 [23••] -MDA-	Retrospective review 1992–2013	124	121	21 %	Hyams and LN metastasis are predictors of DFS. Age is a predictor of OS. Modified Kadish is not a predictor of outcome

Compliance with Ethics Guidelines

Conflict of Interest Rami E. Saade, Ehab Y. Hanna, and Diana Bell declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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