Original Investigation

Importance of Tumor Grade in Esthesioneuroblastoma Survival
A Population-Based Analysis

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IMPORTANCE There is a need for larger studies characterizing the effect of tumor grade on survival for patients with esthesioneuroblastoma.

OBJECTIVE To investigate prognostic factors for survival in patients diagnosed with esthesioneuroblastoma, including emphasis on tumor grade.

DESIGN, SETTING, AND PARTICIPANTS Retrospective, population-based cohort study of patients in the Surveillance, Epidemiology, and End Results (SEER) tumor registry who were diagnosed with esthesioneuroblastoma from January 1, 1973, to January 1, 2010. The last date of survival follow-up was 2013.

MAIN OUTCOMES AND MEASURES Overall and disease-specific survival.

RESULTS The cohort included 281 patients with a mean age of 52 years. There were 154 males (54.8%) and 127 females (45.2%). Kaplan-Meier analysis demonstrated an overall and disease-specific survival rate of 61% and 70% at 5 years and 50% and 64% at 10 years, respectively. Multivariable Cox regression analysis showed that advanced tumor grade and modified Kadish stage (hazard ratio, 4.930; 95% CI, 2.635-9.223; $P = .001$) portended worse disease-specific survival, and radiation therapy (hazard ratio, 0.499; 95% CI, 0.272-0.916; $P = .03$) improved disease-specific survival. Patients with low-grade tumors (grades I and II) demonstrated an overall and disease-specific survival rate of 84% and 92% at 5 years and 67% and 87% at 10 years, respectively. Multivariable analysis of low-grade tumors only revealed receiving surgery ($P = .004$) as an independent positive predictor of disease-specific survival. High-grade tumors (grades III and IV) demonstrated overall and disease-specific survival of 40% and 50% at 5 years and 34% and 43% at 10 years, respectively. Multivariable analysis of high-grade tumors showed modified Kadish stage (hazard ratio, 2.025; 95% CI, 1.430-2.866; $P < .001$) predicted worse disease-specific survival, and radiation therapy (hazard ratio, 0.433; 95% CI, 0.228-0.864; $P = .02$) independently predicted improved disease-specific survival.

CONCLUSIONS AND RELEVANCE Here, to our knowledge, we report the largest study investigating prognostic factors for survival, with the inclusion of tumor grade, in patients diagnosed with esthesioneuroblastoma. Patients with high-grade tumors had substantially worse survival rates than patients with low-grade tumors. Multivariable analysis revealed only receiving surgery as an independent predictor of disease-specific survival for patients with low-grade tumors, while modified Kadish stage and postoperative radiation therapy were significant factors in predicting disease-specific survival in patients with high-grade tumors. This study highlights the growing evidence that tumor grade should be a key factor in predicting survival in patients with esthesioneuroblastoma, and that adjuvant radiation therapy improves survival rates among patients with high-grade, but not low-grade, tumors.

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Esthesioneuroblastoma, also known as olfactory neuroblastoma (ONB), is a rare tumor thought to originate from the olfactory neuroepithelium in the superior nasal vault. Because of its rarity, to our knowledge, there have been no prospective, randomized clinical trials investigating optimal treatment regimens. Therefore, treatment guidelines must be extrapolated from grouped institutional experiences or population-based tumor registries. Current treatment guidelines recommend wide local excision via open or endoscopic craniofacial resection with postoperative radiation therapy.[1-5] The role of chemotherapy is less studied, but is generally reserved for advanced disease in the neoadjuvant or adjuvant setting.[6]

Experiences from many institutions have begun to highlight the distinct clinical behavior of high- and low-grade ONB. Our series (although the results are not shown) and the experiences of other institutions[7,8] have begun to highlight the distinct clinical behavior of high- and low-grade ONB. Here, to our knowledge, we report results of the largest population-based study investigating the importance of tumor grade on outcome in ONB and aim to identify distinct prognostic factors for survival between high- and low-grade ONB.

Methods

A retrospective study was performed using the Surveillance, Epidemiology, and End Results (SEER) tumor registry database.[9] The National Cancer Institute does not require institutional review board approval for this deidentified registry. The public-use database from the SEER 18 (1973-2010) registry was used to extract appropriate cases. The SEER database is composed of cancer registries that are thought to include approximately 10% of the US population and is the primary source of national estimates of cancer incidence and survival. Use of the database has been validated for clinical outcomes research.[10]

The SEER database codes information regarding the primary site and extent of disease. All patients diagnosed with ONB from January 1, 1973, through January 1, 2010, were identified using histologic feature code 9522. Site-specific codes were used to confirm that the tumor originated in the nasal cavity or paranasal sinuses. Cases with a histologic ONB code that were located at sites outside the nasal cavity or paranasal sinuses were considered a coding error and excluded from analysis. The addition of tumor grade to ONB in the SEER database has only been consistently reported in the last 2 decades. Therefore, only patients with information regarding tumor grade were included in this study. Tumor grade is reported on a scale from I to IV in the SEER database and, for the purposes of this study, low-grade tumors included grades I and II and high-grade tumors represented grades III and IV.

No specific staging information such as Dulguerov-Calcaterra or modified Kadish staging was available for these cases; however, related disease information, including SEER historic stage, collaborative stage extension, extent of disease, and primary site, allowed for deduction of modified Kadish staging. This method of modified Kadish stage derivation has been used previously for SEER studies pertaining to ONB.[2] Briefly, the modified Kadish stage was derived for each case using the extent of disease and collaborative staging data sets available through the SEER database case-listing search. Extent of disease and collaborative staging extent codes for anatomic involvement of primary tumors were grouped and correlated with the appropriate modified Kadish stage as follows: confined to the nasal cavity (stage A), extension to the paranasal sinuses (stage B), extension beyond the nasal cavity and sinuses, including the cribriform plate and base of skull (stage C), and lymph node and distant metastases (stage D). Cases with unknown or ambiguous extent of disease and collaborative staging extent codes were not assigned a stage according to the modified Kadish system and were excluded from analysis.

Primary outcomes included overall survival (OS) and disease-specific survival (DSS), with the last date of survival follow-up in 2013. *Overall survival* was defined as the time from initial treatment to death from any cause. *Disease-specific survival* was defined as the time to death directly attributable to the primary malignant tumor, as reported in the SEER database. Kaplan-Meier curves were constructed to visualize OS and DSS rates between groups. The differences were formally tested for using the log-rank test. Covariates were assessed for predictive performance with univariable and multivariable Cox proportional hazards regression models with regard to OS and DSS. Comparisons between groups were deemed statistically significant at $P < .05$. Covariates were chosen for multivariable analysis based on factors identified as significant or near significant on univariable analysis ($P < .20$; log-rank test). This method was chosen to minimize the total number of covariates, thus improving the generalizability of the findings and minimizing instability in the model. As a default, age and sex were included in all multivariable models. Using this method, there were no less than 10 events per covariate for each model. Statistical analyses were performed in SPSS, version 21 (IBM Corporation).

Results

A total of 705 patient records were initially extracted from the SEER database, including those of patients with ONB diagnosed from January 1, 1973, through January 1, 2010. Information regarding tumor grade has only been consistently reported in the SEER database in the last decade. This resulted in 291 patients with information regarding tumor grade. A total of 281 patients had sufficient clinical data to apply the modified Kadish staging system (**Table 1**). Therefore, the final study cohort included 281 patients, of which 154 (54.8%) were male and 127 (45.2%) were female. The mean age was 52 years (range, 3-88 years). The median follow-up time was 40 months (range, 0-330 months). A total of 81.5% of patients were white, 9.6% were African American, and 8.8% were of another race or ethnicity. Fifty patients' tumors (17.8%) were Kadish stage A, 50 (17.8%) were stage B, 75 (26.7%) were stage C, and 106 (37.7%) were stage D. A total of 135 patients (48.0%) had low-grade tumors and 146 (52.0%) had high-grade tumors. Information re-

Table 1. Patient Demographics, Tumor Characteristics, and Treatment Modality

Characteristic	Value[a]
Sex	
Female	127 (45.2)
Male	154 (54.8)
Age, y	
Mean	52
Median (range)	52 (3-88)
Race	
White	229 (81.5)
African American	27 (9.6)
Asian	17 (6.0)
Native Hawaiian/Pacific Islander	4 (1.4)
American Indian	2 (0.7)
Other	2 (0.7)
Kadish stage	
A	50 (17.8)
B	50 (17.8)
C	75 (26.7)
D	106 (37.7)
Tumor grade	
Low	135 (48.0)
High	146 (52.0)
Lymph node involvement	
Positive	26 (9.3)
Negative	199 (70.8)
Unknown	56 (19.9)
Received surgery	
Yes	230 (81.9)
No	49 (17.4)
Unknown	2 (0.7)
Received radiation therapy	
Yes	122 (43.4)
No	169 (56.6)

[a] Values are expressed as number (percentage) unless otherwise specified.

garding lymph node status at diagnosis was available for 225 patients, of whom 26 (9.3%) had presence of neck disease and 199 (70.8%) did not. A total of 230 patients (81.9%) received surgery while 49 (17.4%) did not. A total of 122 patients (43.4%) received radiation therapy either postoperatively or primarily while 159 (56.6%) did not.

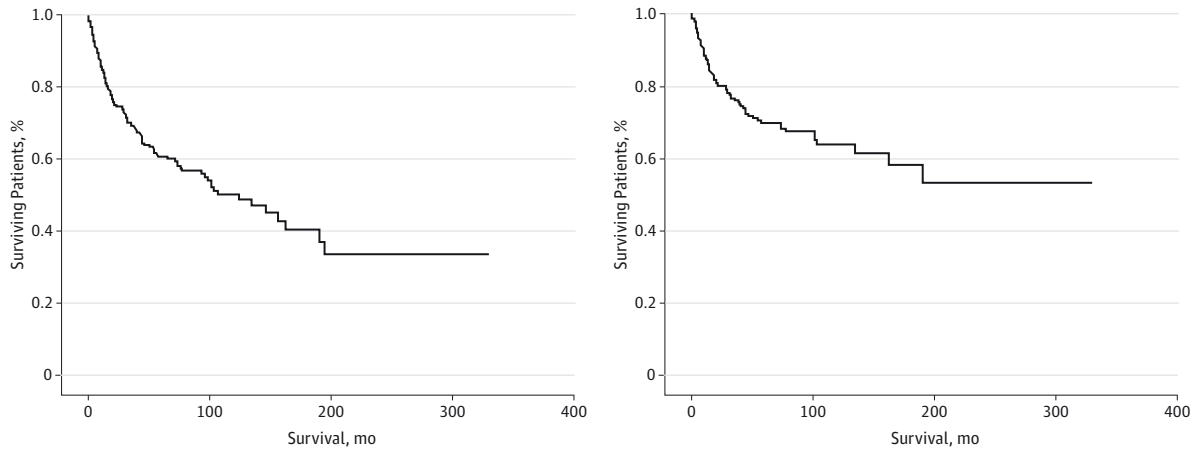
Factors Predicting Survival

Kaplan-Meier analysis demonstrated OS and DSS of 61% and 70% at 5 years and 50% and 64% at 10 years, respectively (**Figure 1**). Univariable analysis of the entire cohort revealed race (P = .02; log-rank test), sex (P = .001; log-rank test), presence of neck disease (P < .001; log-rank test), radiation therapy (P = .01; log-rank test), receiving surgery (P < .001; log-rank test), tumor grade (P < .001; log-rank test), and modified Kadish stage (P < .001; log-rank test) to be predictors of OS. Sex (P = .02; log-rank test), presence of neck disease (P < .001; log-rank test), radiation therapy (P < .001; log-rank test), receiving surgery (P < .001; log-rank test), tumor grade (P < .001; log-rank test), and Kadish stage (P < .001; log-rank test) were predictors of DSS. Multivariable Cox regression analysis (**Table 2**) revealed advanced age, tumor grade, and modified Kadish stage to be independent negative predictors of OS while female sex independently predicted better OS. Advanced tumor grade and modified Kadish stage independently predicted worse DSS. Radiation therapy independently predicted better DSS.

Factors Predicting Survival With Low-Grade Tumors

Analysis of low-grade tumors (n = 135) by univariable analysis revealed sex (P = .01; log-rank test) and surgery (P = .04; log-rank test) to be predictors of OS, and presence of neck disease (P = .01; log-rank test) and receiving surgery (P < .001; log-rank test) to be predictors of DSS. Multivariable analysis (incorporating age, sex, presence of neck disease, and receiving surgery as covariates) revealed age (hazard ratio, 1.062; 95% CI, 1.030-1.094; P < .001), receiving surgery (hazard ratio, 0.244; 95% CI, 0.080-0.747; P = .01), and sex (hazard ratio, 0.277; 95%

Figure 1. Overall and Disease-Specific Survival for Cohort



A, Kaplan-Meier estimates of overall survival. B, Kaplan-Meier estimates of disease-specific survival.

Table 2. Multivariable Cox-Regression Analysis of Factors Affecting Overall and Disease-Specific Survival

Factor	Overall Survival[a]	*P* Value	Disease-Specific Survival[a]	*P* Value
Age	1.024 (1.012-1.037)	.001	1.013 (0.999-1.029)	.07
Sex	0.576 (0.387-0.856)	.006	0.689 (0.431-1.102)	.12
Race	0.950 (0.727-1.241)	.71	0.764 (0.272-0.916)	.16
Presence of neck disease	1.194 (0.967-1.474)	.10	1.106 (0.849-1.442)	.46
Received radiation	0.701 (0.433-1.136)	.15	0.499 (0.272-0.916)	.03
Received surgery	0.885 (0.510-1.535)	.66	0.779 (0.415-1.460)	.44
Tumor grade	3.144 (2.018-4.899)	.001	4.930 (2.635-9.223)	.001
Kadish stage	1.436 (1.115-1.786)	.001	1.905 (1.411-2.572)	.001

[a] Values are presented as hazard ratio (95% CI).

CI, 0.117-0.656; *P* = .04) to be independent predictors of OS. Multivariable analysis of low-grade tumors (incorporating modified Kadish stage, presence of neck disease, receiving surgery, age, and sex as covariates) only revealed receiving surgery (hazard ratio, 0.135; 95% CI, 0.035-0.521; *P* = .004) to be an independent predictor of DSS.

Factors Predicting Survival With High-Grade Tumors

Univariable analysis of high-grade tumors (n = 146) revealed presence of neck disease (*P* = .001; log-rank test), receiving surgery (*P* = .02; log-rank test), and modified Kadish stage (*P* < .001; log-rank test) as predictors of OS, and presence of neck disease (*P* < .001; log-rank test), radiation therapy (*P* = .02; log-rank test), receiving surgery (*P* = .006; log-rank test) and modified Kadish stage (*P* = .001; log-rank test) to be predictors of DSS. Multivariable analysis (incorporating age, sex, race, presence of neck disease, radiation therapy, receiving surgery, and modified Kadish stage as covariates) revealed age (hazard ratio, 1.016; 95% CI, 1.003-1.029; *P* = .02) and modified Kadish stage (hazard ratio, 1.710; 95% CI, 1.286-2.274; *P* < .001) to be independent predictors of OS and modified Kadish stage (hazard ratio, 2.025; 95% CI, 1.430-2.866; *P* < .001) and radiation therapy (hazard ratio, 0.433; 95% CI, 0.228-0.864; *P* = .02) to be independent predictors of DSS.

Discussion

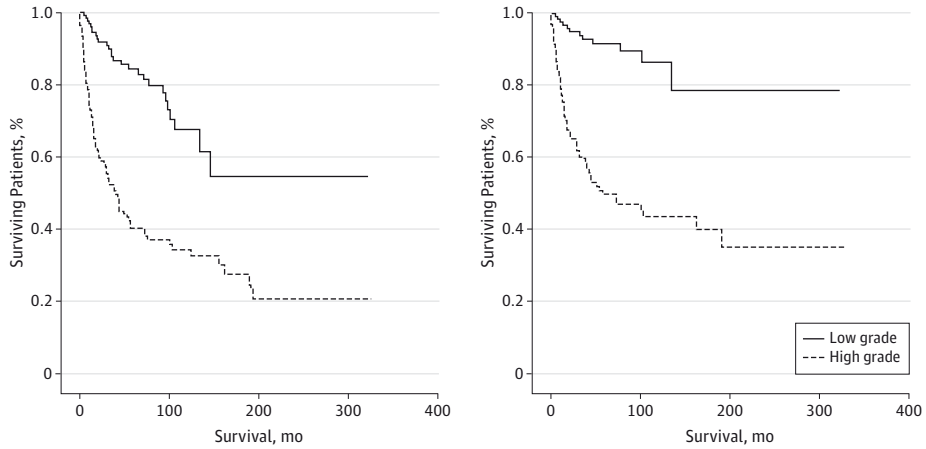
Esthesioneuroblastoma is a rare malignant tumor of the superior nasal vault. Treatment guidelines are constantly evolving owing to innovation in surgical access and improvement in pathologic evaluation. A particular area of controversy is the prognostic significance of tumor grade in ONB outcome. This article represents, to our knowledge, the largest population-based study evaluating prognostic factors for survival in patients with ONB with the inclusion of tumor grade.

Numerous studies have attempted to identify prognostic factors for survival for patients with ONB. One of the largest series[5] was an international collaborative study involving 151 patients that investigated outcomes after craniofacial surgery for ONB. Using multivariable analysis, intracranial extension and positive surgical margins were identified to be independent predictors of worse overall, disease-specific, and recurrence-free survival. Other studies have identified the Kadish system, T staging of Dulguerov-Calcaterra, tumor grade, nodal involvement, and radiation dose to also be factors.[3,4,11] In this study, multivariable Cox regression analysis revealed advanced age, tumor grade, and modified Kadish stage to be negative independent predictors of OS, while female sex independently predicted better OS. The effect of age and sex on all-cause survival is expected in this analysis because the OS rate includes extraneous deaths from expected age-related mortality. This issue is circumvented when reporting DSS. In this study, advanced tumor grade and modified Kadish stage independently predicted worse DSS, while radiation therapy independently predicted better DSS. Age and sex had no influence on DSS. These findings agree with prior published studies.[3-5]

Pathologic grading of ONB is by Hyams criteria, which groups tumors on a scale of I to IV based on histologic features that roughly represent a spectrum of benign to malignant behavior. Briefly, Hyams grade I tumors display preserved lobular architecture, zero mitotic index, no nuclear polymorphisms, prominent fibrillary matrix, no evidence of necrosis, and cells loosely organized around a central fibrillar eosinophilic material (Homer-Wright pseudorosettes). Hyams grade II tumors have similar findings to grade I but have evidence of low levels of mitoses and nuclear polymorphisms. Hyams grade III tumors begin to have reduced lobular architecture, a moderate mitotic index with moderate levels of nuclear polymorphisms, and a reduction in fibrillary matrix. Flexner-Wintersteiner rosettes, which are true rosettes with cells arranged around an empty space, may be present in Hyams grade III tumors. Hyams grade IV tumors show a high mitotic index and nuclear polymorphism, no fibrillary matrix and rosettes, and frequent necrosis.[7]

Because of the low power of institutional articles, prognostication by tumor grade has provided varied results.[12,13] Kane et al[14] performed a systematic review of 956 patients from 205 studies that reported ONB outcomes. Using univariable analysis, their investigation revealed worse survival in patients with Kadish stage C tumors and Hyams grade III or IV tumors, and in patients older than 65 years. Multivariable analysis demonstrated that Hyams grade III or IV tumors carried significant risk (hazard ratio, 4.83; *P* < .001). In addition, they concluded that the biological behavior of ONB could be summarized as representing 2 patterns: low grade (Hyams grade I or II) and high grade (Hyams grade III or IV). This hypothesis was supported in a follow-up study[7] that investigated 20 patients with Kadish stage C tumors in which patients with low-grade tumors demonstrated improved 2-year

Figure 2. Overall and Disease-Specific Survival by Tumor Grade



A, Kaplan-Meier estimates of overall survival for low- and high-grade tumors. B, Kaplan-Meier estimates of disease-specific survival for low- and high-grade tumors. $P < .001$; log-rank test.

progression-free survival compared with patients with high-grade tumors (86% vs 49%). Furthermore, the authors concluded that tumor grade appeared to be the best method to select patients for adjuvant radiotherapy among patients with Kadish stage C tumors. One of the largest institutional studies,[8] which included 109 patients, also supported distinct natural history for low- and high-grade ONB tumors. In addition to reporting worse OS for patients with high-grade pathologic features, they showed that high-grade tumors correlated with more advanced localized disease as well as regional neck metastasis.

The large sample size in our study provided sufficient power to more thoroughly understand the natural history of low- and high-grade lesions. In addition, multivariable analysis was able to statistically assess the effect of treatment modality and adjuvant therapy. Our study confirms prior findings and reports substantially worse OS and DSS for high-grade tumors (**Figure 2**). A powerful addition to the literature is the divergent prognostic factors for survival identified between low- and high-grade lesions in this study. As reported in this study, multivariable analysis of high-grade tumors revealed advanced modified Kadish stage (hazard ratio, 2.025; $P < .001$) to be a negative independent predictor of DSS, and radiation therapy (hazard ratio, 0.433; $P = .02$) to be a positive independent predictor of DSS. This finding supports the current impression that high-grade pathologic features should warrant combination therapy.[7] In contrast with high-grade tumors, multivariable analysis of low-grade tumors only revealed receiving surgery (hazard ratio, 0.135; $P = .004$) to be a positive independent predictor for DSS, while radiation therapy had no effect on OS and DSS for low-grade tumors ($P = .22$ and .23, respectively; log-rank test). This suggests that, for low-grade tumors, surgical resection with negative margins may suffice as the optimal treatment, and the morbidity of adjuvant radiation therapy may be avoided. However, care should be taken with this approach because it has been shown that radiation therapy is crucial for local control.[15] Further research is needed to ascertain whether radiation therapy for low-grade lesions provides improved local control.

There are inherent weaknesses in this study that should be acknowledged when reviewing our results, because use of the SEER database is not without its own limitations. First, surgical intervention, as defined by the SEER database, does not provide further details of the extent of resection, nor does it provide a time reference with respect to other treatments, such as radiation. In addition, detailed radiation therapy data are not provided, and there is an inability to differentiate neoadjuvant, concurrent, adjuvant, and palliative radiation therapy. Finally, tumor grade is reported on a scale from I to IV in the SEER database, with grade I designated as well differentiated, grade II as moderately differentiated, grade III as poorly differentiated, and grade IV as undifferentiated. This grading scheme roughly corresponds to the Hyams grading scale and may not be interpreted as a true Hyams grade. Nonetheless, the results are still novel, and variability was minimized in this study by grouping patients into low- and high-grade tumor groups. It is expected that these results will provide the early evidence for multi-institutional series.

Conclusions

The management of esthesioneuroblastoma is constantly evolving because of advances in surgical technique and histopathologic analysis. Here, to our knowledge, we report the largest study confirming a distinct natural history between low- and high-grade esthesioneuroblastoma, with unique prognostic factors for survival. Patients with low-grade lesions had significantly improved survival. Surgery alone predicted improved DSS while radiation therapy had no effect on survival. In contrast, patients with high-grade tumors had improved survival with the addition of radiation therapy.

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Study concept and design: Tajudeen, Suh, Wang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Tajudeen, Arshi, Suh, Wang.
Critical revision of the manuscript for important intellectual content: Tajudeen, Suh, St John, Wang.
Statistical analysis: Tajudeen, St John.
Administrative, technical, or material support: St John, Wang.
Study supervision: Suh, St John, Wang.

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