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Prognostic significance of Kadish staging in esthesioneuroblastoma: An analysis of the National Cancer Database

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Abstract

Background—Given the rarity of esthesioneuroblastoma, it is difficult to validate a staging system. The purpose of this study was to investigate the utility of the Kadish staging system in esthesioneuroblastoma using the National Cancer Database (NCDB).

Methods—One thousand one hundred sixty-seven patients with esthesioneuroblastoma were identified from the NCDB.

Results—Five-year survival was 80.0% for Kadish A, 87.7% for Kadish B, 77.0% for Kadish C, and 49.5% for Kadish D. Kadish B had higher survival than Kadish A. More Kadish B patients received surgery with adjuvant therapy than Kadish A patients (41.6% vs 32.5%; $P = .0038$) and also had more positive margins (21.6% vs 11.3%; $P = .03$). There was no difference in age distribution, sex, race, or neck dissection status between the 2 groups.

Conclusion—Kadish B had greater survival than Kadish A, but the treatment characteristics could not account for this difference. The utility of early-stage Kadish staging is uncertain and requires further study.

Keywords

esthesioneuroblastoma; head and neck cancer; oncology; outcomes; statistics

1. INTRODUCTION

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a rare cancer thought to arise from neuroendocrine cells in the olfactory epithelium. Esthesioneuroblastoma represents about 3%-6% of all cancers in the nasal cavity and paranasal sinuses, although incidence has been hard to determine because of its uncommon nature.¹ Epidemiological numbers may have skewed by past inclusion of sinonasal undifferentiated carcinoma and sinonasal neuroendocrine carcinoma before advent of more accurate histological techniques.²

There are a number of staging systems used for esthesioneuroblastoma. Given the rarity of esthesioneuroblastoma, it is difficult to validate a staging system. The most commonly used staging system is the Kadish staging system. Kadish staging was first introduced in 1976 as the staging method before treatment based on the extension of disease.^{3,4} Alternate staging systems have been proposed by Dulguerov and Calcaterra⁵ and Biller et al,⁶ which use different definitions of disease extent. Previous studies found that the modified Kadish staging system could be a useful predictor in survival.^{1,2} However, in other studies, Kadish staging was not identified as a prognostic factor.^{5,7} Further evaluation of the value of the modified Kadish staging in esthesioneuroblastoma is warranted.

A previous analysis of esthesioneuroblastoma was done by Jethanamest et al¹ using the Surveillance, Epidemiology, and End Results (SEER) database. The SEER study found that modified Kadish stage, lymph node status, and age at diagnosis were predictive of survival. Overall survival at 10 years was 83.4% for patients with stage A disease, 49% for patients with stage B disease, 38.6% with stage C disease, and 13.3% for patients with stage D disease. Combined treatment with surgery and radiotherapy (RT) was also found to have greater statistically significant median survival (216.8 months) than RT alone (53.7 months).⁸ The SEER database compiles data on cancer diagnoses and outcomes from population-based cancer registries that cover 28% of the US population. In contrast, the data in National Cancer Database (NCDB) is identified from the hospitals and captures over 70% of all incident cancers in the United States. It includes more detailed information on tumor characteristics, surgery, RT, and chemotherapy when compared to the SEER database, which is very useful when evaluating a surgically based staging system. This allows for more in-depth study of tumor characteristics, treatment trends, and their influence on survival outcomes.

In this investigation, we sought to analyze the prognostic value of Kadish staging using the NCDB for outcomes related to esthesioneuroblastoma.

2 MATERIALS AND METHODS

2.1 Data source

The NCDB is a national hospital-based cancer registry sponsored by the American College of Surgeon's Commission on Cancer and the American Cancer Society. As previously noted, it includes approximately 70% of newly diagnosed cancer cases in the United States from over 1500 accredited cancer care programs. The database provides extensive information on

patient demographics, extent of disease, and treatment regimens, as well as long-term overall survival.

2.2 Patient population

Patients diagnosed as having olfactory neuroblastoma of the nasal cavity and paranasal sinuses between January 1, 2004, and December 31, 2013, were identified. Given the deidentified nature of patient data, the analysis was exempt from review by our institutional review board. The NCDB was queried for olfactory neuroblastoma cases using International Classification of Diseases for Oncology, Third Edition topography code 9522/3. Overall survival and 5-year survival were investigated as outcomes.

Modified Kadish staging was not available for these cases. However, tumor extension information was derived from the tumor extension variable available in the NCDB. Although only the TNM classification group was available for 258 cases, the tumor extension variable provides information on local extension of the tumor based on clinical and pathological T classification. The cases that were in situ or limited to the septum, floor, lateral wall, meatus, nasal concha, and vestibule with or without bony invasion were considered to be Kadish stage A. Origin in the paranasal sinuses or further extension into the paranasal sinuses and nasoethmoidal complex were considered to be Kadish stage B. Cases with extension into the skull base, palate, cribriform plate, medial wall or floor of orbit, pterygoid plates, nasopharynx, skin, dura, and brain were considered to be Kadish C. Patients with nodal disease or metastatic disease were classified as having Kadish D disease. Any case that did not provide data for the extent of disease could not be staged and was excluded from coding. The modified Kadish stage was successfully determined in 1107 of 1167 cases. TNM classification was available for 258 cases.

Patient demographics (age, race, sex, facility type, Charlson-Deyo score, and insurance), disease characteristics (modified Kadish staging and TNM classification), and treatment variables (type of treatment, neck dissection, and surgical margins) were investigated as predictors of overall survival. Age was separated into a binomial variable of less than 60 years old and equal to and greater than 60 years old. Race was separated into white, black, and other. Facility type was separated into academic and nonacademic centers (combination of community cancer programs, comprehensive community cancer programs, and other programs). The Charlson-Deyo score is reported by the NCDB, in which 0 represents no known comorbid conditions, 1 represents 1 comorbid condition, and 2 represents 2 or more comorbid conditions. Insurance status was divided into private and government insurance (Medicare and Medicaid).

Treatment regimens were separated into chemotherapy alone, RT alone, surgery alone, surgery with adjuvant RT, surgery with adjuvant chemoradiation, surgery with adjuvant chemotherapy, and chemoradiation alone. Regional lymph node surgery, as reported by the NCDB, was considered to constitute neck dissection. Positive margins (combination of microscopic residual tumor, macroscopic residual tumor, or residual tumor not otherwise specified) and negative margins (no residual tumor with negative margins) were separated. The NCDB defines margin status as positive, negative, or unavailable. Margins were considered to be positive if there was residual tumor within 5 mm of the margin.

2.3 Statistical analysis

All statistical analyses were performed using the SAS software package version 9.3 (SAS System for Windows). Overall patient demographics, tumor characteristics, treatment factors, and outcomes were compiled using standard summary statistics. Kaplan-Meier analysis and the log-rank test were performed to determine the unadjusted association between overall survival and age, sex, insurance status (as a measure of socioeconomic status), metastatic disease, treatment, and margin status among the entire cohort. The Pearson chi-square and Fisher's exact tests were used to determine the association between categorical variables and different staging groups. Multivariable analysis was conducted by Cox logistic regression. Survival effects of covariates were reported as hazard ratios (HRs). Probability values (*P* values) of $< .05$ were used to indicate statistical significance for all comparisons.

3 RESULTS

Of the cohort, 1167 patients met inclusion criteria. Patient demographics, disease characteristics, and treatment factors are listed in Table 1. The median age of diagnosis was 54.0 years (range 18-90 years). Men represented 60.5% of the patients, whereas women represented 39.5% of the patients. White patients accounted for the majority of cases (84.0%). Of the patients, 64.1% were treated at academic centers, whereas 36.0% were treated at nonacademic centers. Over 50% of the patients had Kadish stage C disease.

3.1 Staging

Survival for the 1107 patients with Kadish staging is presented in Table 2. The 5-year overall survival rate was 77.4% and the 10-year survival was 67.3%. The 5-year survival was 80.0% for Kadish stage A, 87.7% for Kadish stage B, 77.0% for Kadish stage C, and 49.5% for Kadish stage D (see Figure 1). The 10-year survival was 68.0% for Kadish stage A, 82.6% for Kadish stage B, 65.4% for Kadish stage C, and 39.7% for Kadish stage D (see Figure 1). To further evaluate the discrepancy in Kadish stage and survival, variables were compared between Kadish A and Kadish B (Table 3). The differences between Kadish stages A and B are highlighted here as the Kadish stage B group had a greater survival than Kadish stage A (87.7% vs 80%; $P < .0001$). More Kadish B patients received surgery with adjuvant therapy compared with Kadish A patients (41.6% vs 32.5%; $P = .0038$). More patients in the Kadish stage B group also had positive margin status than Kadish stage A patients (13.1% vs 8.1%; $P = .03$). There was no difference in age distribution, sex, race, or neck dissection status between the 2 groups.

Survival for TNM classification was also evaluated. Five-year survival was 91.8% for stage 1, 88.3% for stage 2, 85.6% for stage 3, 83.3% for stage 4, 58.6% for stage 4A, 71.1% for stage 4B, and 27.3% for stage 4C.

3.2 Treatment modalities

In the whole cohort, there was no difference in 5-year overall survival between the surgery and surgery with adjuvant radiation groups (81.2% vs 85.4%; $P = 0.99$). In Kadish stage A, there was no survival difference between surgery alone and surgery with adjuvant radiation

($P = .98$). This lack of survival difference persisted in Kadish stage B ($P = .26$). There was no difference in the median radiation dose between Kadish stages A and B (60.0 Gy [range 54.0-105.0] vs 60.0 Gy [range 50.4-111.6]; $P = .32$) in the cohort that was treated with surgery with adjuvant radiation.

3.3 Prognostic factors and multivariate analysis

Age less than 60 years, female sex, having private insurance, and negative margins after surgery were associated with improved survival on univariate analysis when compared to age greater than 60 years, male sex, having government insurance, and positive margin status, respectively (Table 2).

Multivariate analysis was done using demographic variables and treatment variables. Age and insurance status were correlated as were the type of treatment and margin status, and were included as they were deemed to be clinically important. Results showed that age less than 60 years (HR 0.47 [confidence interval (CI) 0.28-0.79]) and negative margins (HR 0.62 [CI 0.40-0.96]) were associated with improved survival, whereas having government insurance was associated with worse survival (HR 1.73 [CI 1.01-2.96]; Table 2). Sex, which was associated with survival during the univariate analysis, was not independently associated with survival on multivariate analysis.

4 DISCUSSION

Esthesioneuroblastoma represents approximately 5% of all malignant sinonasal tumors. Because of its rarity, much of the available literature available is comprised of smaller retrospective institutional studies. In this cohort, 5-year overall survival was 77.4%, which is comparable to previous retrospective studies that had survival rates from 62.1%-89%.^{1,9,10} There is no standardized staging system for esthesioneuroblastoma as it is difficult to determine the prognostic ability of each staging system. Kadish staging³ is the most commonly used of the different staging systems, and, therefore, has been helpful in comparing similar tumors. The prognostic value of Kadish staging has been supported by several studies,^{1,2,11,12} but the prognosis for each stage is inconsistent among studies, likely because of the small patient numbers per stage.

A meta-analysis of 390 patients reported 72% for the 5-year survival in Kadish A tumors, 59% survival in Kadish B tumors, and 47% in Kadish C tumors.² However, a rare cancer network study reviewed 77 cases from several institutions and found a much higher survival prognosis for Kadish stage B with survival of 76%, 80% in Kadish A, and 52% in Kadish C tumors.¹¹ Other studies have not found a survival correlation based on Kadish staging.^{5,7} In a review of 21 patients, Kadish stages B and C tumors had similar overall survival, 71.4% and 75%, respectively.⁷

The SEER database study showed 5-year overall survival rates of 93% for Kadish A, 81% for Kadish B, 66% for Kadish C, and 47% for Kadish D tumors. However, the Kadish stage C group only had 10 cases, limiting comparative analyses.¹ The NCDB offers more detailed information on tumor characteristics and treatment when compared to the SEER database. Therefore, we were able to evaluate Kadish staging and its influence on survival outcomes

using the NCDB. In our cohort, 5-year survival was 80.0% for Kadish stage A, 87.7% for Kadish stage B, 77.0% for Kadish stage C, and 49.5% for Kadish stage D. These results show a survival difference between Kadish stages A and B that is not dependent on advancing Kadish stage.

There may be several explanations behind our paradoxical finding of Kadish B tumors having greater overall survival than Kadish A tumors in the NCDB. First, there are inherent limitations to the NCDB database. Although the NCDB provides extensive information on patient demographics, extent of disease, treatment regimens, as well as long-term overall survival, one cannot verify the fidelity of the data input and, thus, may affect data output and conclusions made. We rely on the proper coding and accurate diagnosis of cases to obtain our cohort and code for modified Kadish staging. The database also does not include local recurrence data, and, therefore, we are unable to assess local control after treatment.

Importantly, there is a component of selection bias in the treatment of Kadish B patients. As Kadish B tumors are considered to be later stage, these patients may be receiving more aggressive treatment regimens, which thereby leads to greater survival. It is possible that Kadish B patients are undergoing more aggressive surgery, such as bilateral resection over unilateral resection or complete dural resections with olfactory bulb resection over dural sampling. The Kadish B cohort also had a greater rate of adjuvant therapy after surgical resection than Kadish A.

Additionally, there may be additional selection biases that are hard to tease out from the dataset. For instance, Kadish A tumors may be more likely to be operated on by surgeons not necessarily trained in oncologic resection given that they are limited to the nasal cavity on imaging. In addition, the cases represented in the NCDB were treated by physicians from many different centers with different philosophies and training and using several treatment algorithms for Kadish A and B tumors, likely making this a heterogeneous cohort.

Despite these potential biases, one may also conclude that there is an inherent flaw in the modified Kadish staging system. Limitations of the modified Kadish staging system have been previously proposed in the literature. One proposed limitation of the Kadish staging system is that olfactory neuroblastoma rapidly spreads to the sinuses, leading to very few cases diagnosed at Kadish stage A.⁵ Another limitation of the Kadish staging system is the grouping of all tumors beyond the nasal cavity and paranasal sinuses as Kadish stage C.⁵ This broad definition restricts discrimination of survival with tumor extension to specific anatomic landmarks. Several institutional reviews found that orbital and intracranial involvement were independent predictors of survival upon Cox regression.^{10,13} The 5-year disease-specific survival was 55.6% with periosteal involvement of the orbit and 88.3% without orbital involvement. Similarly, survival fell to 41.7% with intracranial involvement.¹⁰ In addition, we propose that, although Kadish A and B tumors differ by origin or extension into the paranasal sinuses, there may not be a pathological distinction. Almost all of the tumors are attached to or have a pedicle in the cribriform plate, which may be more prognostic of survival than extension into the sinuses. In all, discrepancies between large databases, such as SEER and the NCDB, as well as smaller studies, indicate the need for

further studies in the forms of meta-analysis and a multi-institutional review for early-stage Kadish tumors, which we have begun.

The prognostic indication of Kadish staging may be further confounded by histological grade. Hyams grade has been shown to be an independent prognostic indicator of survival when separated into low-grade and high-grade.¹⁴ Hyams grade was not available in the NCDB. A meta-analysis found that Kadish staging predicted survival unless considered in conjunction with Hyams grade, when it was no longer predictive. However, Hyams grade was independently predictive of survival, with higher grade indicating worse survival.¹⁵ As Hyams grade requires surgical biopsy, it is more difficult to obtain. However, as the study found that 14% of Kadish A tumors were of high Hyams grade, it may be important to determine histological grade for more accurate prediction.¹⁵

Other staging systems have also been shown to be predictors of survival in a limited number of studies. In the original study in which the Dulguerov TNM classification was proposed, it was found to be a better predictor of survival than the Billings and Kadish staging.⁵ In another institutional review, modified Dulguerov TNM classification, in addition to Hyams grade, were the only 2 independent predictors.¹⁴ There was not enough information available in the NCDB to compare the different staging systems, including TNM classification.

Based on the results of this study indicating that modified Kadish staging may not be prognostic and on our own experience, we believe that there may not be a distinction between Kadish stage A and Kadish stage B. Most cases of esthesioneuroblastoma originate from the cribriform plate, which is the attachment point in nearly all cases. We believe treatment of these tumors depends on successful oncologic resection of the tumor attachment point. These early-stage tumors often fill the nasal cavity and extend toward other sinuses, however, often times there are no direct extensions of the tumor into the surrounding mucosa as these tumors to expand into these structures and not invade.

Survival with different modalities of treatment of esthesioneuroblastoma is not clear because of the low patient numbers. Overall survival rates are also inconsistent between numerous cohort and institutional studies. Although a combination of surgery and radiation has been used most frequently and has been shown to have a survival around 65%, many patients are still being treated by surgery or RT alone as no statistically significant difference has been shown for the different treatment modalities.^{2,10,13,16} In our overall cohort, there was also no difference in survival between the surgery alone and the surgery with adjuvant radiation groups. When surgery alone and surgery with adjuvant radiation were compared among the different Kadish stages, there was also no difference in survival between the 2 groups in Kadish stages A, B, and D. However, for patients with Kadish stage C, surgery with adjuvant radiation had better survival than surgery alone (84.0% vs 71.3%; $P = .038$). As the Kadish staging was not prognostic of survival in this entire cohort, the treatment difference may not be indicative of actual therapeutic effect.

5 CONCLUSION

Kadish staging is the most commonly used staging system for esthesioneuroblastoma. The rarity of the disease makes it difficult to validate a staging system, and the prognostic value of Kadish staging is unclear from numerous large and small studies. In this analysis, Kadish stage did not correlate with survival for early-stage disease. Although there are inherent limitations to NCDB database, neither patient characteristics nor treatment difference could account for this discrepancy. The prognostic significance of the distinction between Kadish A versus B warrants further investigation in a multi-institutional format.

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The Commission on Cancer's NCDB and the hospitals participating in the Commission on Cancer NCDB are the sources of the deidentified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

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FIGURE 1.
Kaplan-Meier curves of overall survival by modified Kadish stage ($P < .0001$)

TABLE 1

Patient demographics, disease characteristics, and treatment factors

Variables	No. of patients (%) n = 1167
Patient demographics	
Age, y, mean	
<60	762 (65.3)
60	405 (34.7)
Race	
White	980 (84.0)
Black	84 (7.2)
Other	103 (8.8)
Sex	
Male	706 (60.5)
Female	461 (39.5)
Charlson-Deyo score	
0	1018 (87.2)
1	122 (10.5)
2	27 (2.3)
Facility	
Nonacademic	353 (36.0)
Academic	629 (64.0)
Insurance status	
Government, Medicaid, Medicare, other government	331 (28.3)
Private	750 (64.3)
Other, not insured, unknown	86 (7.4)
Disease characteristics	
Kadish staging	
Stage A	173 (14.8)
Stage B	221 (18.9)
Stage C	621 (53.2)
Stage D	92 (7.9)
Unknown	60 (5.1)
TNM clinical classification group	
0	1 (0.1)
1	54 (4.6)
2	37 (3.2)
3	37 (3.2)
4	12 (1.0)
4A	58 (5.0)
4B	48 (4.1)
4C	11 (0.9)

Variables	No. of patients (%) n = 1167
Unknown	907 (77.9)
Treatment factors	
Treatment	
Chemotherapy alone	23 (2.0)
RT alone	16 (1.4)
Surgery alone	268 (24.1)
Surgery + adjuvant RT	404 (36.3)
Surgery + adjuvant chemoradiotherapy	300 (27.0)
Surgery + adjuvant chemotherapy	17 (1.5)
Chemotherapy 1 RT	62 (5.6)
Induction therapy	25 (2.1)
Neck dissection	
Yes	75 (6.4)
No	1045 (89.6)
Unknown	47 (4.0)
Margins	
Positive	215 (18.4)
Negative	481 (41.2)
Unknown	471 (40.4)

Abbreviation: RT, radiotherapy.

TABLE 2

Univariate survival and multivariate analysis

Variables	5-y overall survival, % (SE)	P value	HR (95% CI)	P value
Overall	77.4 (1.5)			
Patient demographics				
Age, y		<.0001		.0048
<60	81.7 (1.7)		0.47 (0.28-0.79)	
60	68.0 (2.9)		1 (Ref)	
Sex		.0291		.2352
Male	74.3 (2.0)		1.30 (0.84-2.02)	
Female	80.9 (2.2)		1 (Ref)	
Facility		.9836		.2311
Nonacademic	77.8 (2.6)		0.75 (0.47-1.20)	
Academic	76.8 (2.1)		1 (Ref)	
Insurance status		<.0001		.0453
Government, Medicaid, Medicare, other government	65.1 (3.3)		1.73 (1.01-2.96)	
Private	81.6 (1.7)		1 (Ref)	
Disease characteristics				
Kadish staging		<.0001		.0007
Stage A	80.0 (4.4)		0.37 (0.16-0.87)	
Stage B	87.7 (2.5)		0.17 (0.07-0.40)	
Stage C	77.0 (2.1)		0.36 (0.19-0.67)	
Stage D	49.5 (6.2)		1 (Ref)	
TNM clinical classification group		<.0001		
1	91.8 (4.0)			
2	88.3 (5.5)			
3	85.6 (6.0)			
4	83.3 (10.8)			
4A	58.6 (6.7)			
4B	71.1 (6.8)			
4C	27.3 (13.4)			
Treatment factors				
Treatment		.9999		.9095
Surgery alone	81.2 (3.0)		0.83 (0.43-1.60)	
Surgery 1 adjuvant RT	85.4 (2.3)		0.83 (0.49-1.40)	
Neck dissection		.0296		.5254
No	78.3 (1.6)		0.50 (0.15-1.66)	
Yes	58.0 (7.6)		0.50 (0.12-2.09)	
Margins		.0005		.0302
Negative	83.6 (2.1)		0.62 (0.40-0.96)	
Positive	73.7 (3.7)		1 (Ref)	

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy.

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TABLE 3

Differences between Kadish A and B

	Kadish A		Kadish B		P value
	No. of patients	%	No. of patients	%	
Age, y					.0884
<60	117	67.63	131	59.28	
60	56	32.37	90	40.72	
Charlson-Deyo score					.7217
0	154	89.02	201	90.95	
1	15	8.67	17	7.69	
2	4	2.31	3	1.36	
Facility type					.0846
Nonacademic	53	30.64	89	40.27	
Academic/research	88	50.87	100	45.25	
Insurance status					.1953
Government	42	24.28	69	31.22	
Private	123	71.10	138	62.44	
Other	8	4.62	14	6.33	
Neck dissection					.1336
No	168	97.11	205	92.76	
Yes	1	0.58	6	2.71	
Unknown	4	2.31	10	4.52	
Treatment					.0238
RT only	2	1.20	5	2.34	
Chemotherapy external RT	3	1.81	7	3.27	
Surgery only	84	50.60	70	32.71	
Surgery + RT	54	32.53	89	41.59	
Surgery + RT + chemotherapy	20	12.05	38	17.76	

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	Kadish A		Kadish B		P value
	No. of patients	%	No. of patients	%	
Margins					.0258
Negative	110	63.58	105	47.51	
Positive	14	8.09	29	13.12	

Abbreviation: RT, radiotherapy.