Objectives: To investigate the characteristics associated with survival in esthesioneuroblastoma and to determine whether the modified Kadish staging system can predict outcome.

Design: Retrospective population-based cohort study.

Subjects: All patients in the Surveillance, Epidemiology, and End Results tumor registry diagnosed as having esthesioneuroblastoma (1973-2002).

Main Outcome Measures: The modified Kadish stage and the overall and disease-specific survival rates were determined.

Results: The cohort included 311 patients with a mean age of 53 years and a unimodal age distribution. The overall 5- and 10-year survival rates were 62.1% and 45.6%, respectively. The modified Kadish staging system was applied to 261 patients. Kaplan-Meier analysis showed the overall and disease-specific survival rates at 10 years to be 83.4% and 90%, respectively, for patients with stage A disease; 49% and 68.3% for patients with stage B disease; 38.6% and 66.7% for patients with stage C disease; and 13.3% and 35.6% for patients with stage D disease. Log-rank test comparisons found Kadish stage (P < .01), treatment modality (P < .002), lymph node status (P < .01), and age at diagnosis (P < .001) to be significant predictors of survival. Cox regression analysis confirmed that Kadish stage remained a significant predictor of disease-specific survival.

Conclusion: The modified Kadish staging system, lymph node status, treatment modality, and age are useful predictors of survival in patients who present with esthesioneuroblastoma.

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Esthesioneuroblastoma (ENB) is a rare tumor of the nasal cavity that is believed to be derived from the olfactory neuroepithelium. It was first described by Berger et al in 1924, but because of the uncommon nature of the disease, its clinical characteristics and its impact on survival remain difficult to study. This tumor has also often been referred to as an olfactory neuroblastoma, although the exact cell of origin has not yet been proved.2 One review of the world literature through 1997 found 945 unique cases, while another review from the Armed Forces Institute of Pathology reported 200 cases.3,4 Esthesioneuroblastoma reportedly represents only 3% to 6% of all cancers in the nasal cavity and paranasal sinuses, although the true incidence is difficult to determine, as contemporary histologic techniques are likely increasing detection.3

Although ENB is uncommon, some consistent features of this disease have been established: it has an approximately equal sex distribution; it affects a wide range of age groups; and, over time, it can locally extend to involve the surrounding paranasal sinuses, cribriform plate, and orbits.3,6 The most common site of metastasis is the cervical lymph nodes (10%-33% of patients), while sites of distant metastasis, including the lungs, brain, and bone, are less common.3,7 The disease usually occurs in the fifth to sixth decades of life, although it is unclear whether there is a unimodal or a bimodal peak in incidence by age.5,6

The first and most commonly referenced staging system was developed by Kadish et al.8 This system divides tumors into 3 groups: group A lesions are limited to the nasal cavity; group B lesions involve the nasal cavity and paranasal sinuses; and group C lesions extend beyond the nasal cavity and paranasal sinuses. The modification of this staging system by Morita et al9 established group D for tumors with regional (cervical lymph node) or distant metastases. Other staging sys-
tems have also been used, but no single staging classification has been universally adopted for this tumor to date, as the prognostic utility of each system has not been proved. Part of the difficulty in assessing clinical behavior and survival outcomes for ENB lies in the rarity of the disease as well as in the difficulty of amassing cases in single-institution studies. At present, the largest report of survival with ENB has involved a cohort of 50 patients, with other large series averaging almost 30 patients. To obtain meaningful estimates of survival in ENB, and the prognostic factors that influence patient outcome, we analyzed a large cohort of cases from the Surveillance, Epidemiology, and End Results (SEER) national cancer registry.

A retrospective cohort study was performed using the SEER tumor registry (National Cancer Institute, Bethesda, Md). The National Cancer Institute does not require institutional review board approval for this deidentified data set. The public-use database from SEER 13 (1973-2002) was used to extract appropriate cases. The SEER registry has been successfully used to study survival outcomes in cases involving various malignancies, including those of the nasal cavity, and has proved particularly useful in cases of uncommon diseases.

The SEER database codes information regarding the primary site and extent of disease. All patients diagnosed as having ENB from 1973 to 2002 (histologic type International Classification of Diseases for Oncology, Third Edition, code 9522) with a site-specific code indicating that the primary tumor originated in the nasal cavity or paranasal sinuses were identified and included in the study. One case involving a histologic-type ENB located in the adrenal gland was considered a coding error and was excluded from our analysis.

No ENB-specific staging information, such as Kadish staging, was available for these cases. However, related disease information, including SEER historic stage and American Joint Committee on Cancer stage, was available for a majority of cases. The SEER database describes the historic stage of each case as localized, regional, or distant. The cases of ENB that originated in the nasal cavity or cranial nerve (not otherwise specified) and that did not involve adjacent organs or tissue were considered Kadish stage A. Any of these cases that were coded as anything beyond “localized” disease were ambiguous and were excluded from analysis. Stage B included all tumors that originated from the maxillary, ethmoid, frontal, sphenoid, and accessory sinuses that did not invade superstructures or involve further contiguous extension. Also, tumors that originated in the superior nasopharynx and extended into paranasal sinuses and those that extended from the nasal cavity into adjacent organs and structures were also considered stage B. Tumors that included extent of disease beyond the sinuses, including the orbit or intracranial extension, were considered stage C. Finally, any cases with “distant” disease were considered group D. Any case that did not provide data for extent of disease could not be staged and was excluded from analysis.

The modified Kadish stage was successfully determined in 261 of 311 cases.

In analyzing causes of death, the database provided information about the site of disease but not diagnosis-specific codes. Disease-specific deaths were therefore defined as any deaths caused by tumors in the following locations: nose, nasal cavity, and middle ear; nasopharynx, other oral cavity, and pharynx; brain and other nervous system; or miscellaneous malignant cancer (excluding any patients with second primary malignancies). All data were extracted from the SEER*Stat software program, and a commercially available statistical package (SPSS Version 13.0; SPSS Inc, Chicago, Ill) was used to perform Kaplan-Meier survival analysis with applicable log-rank tests. Cox multivariate regression analysis was then performed, incorporating race, stage, sex, age at diagnosis, year of diagnosis, SEER geographic registry, and treatment modalities used.

The cohort included 311 patients (mean age, 53 years). The age distribution was found to be unimodal, with the majority of patients between 40 and 70 years of age (Figure 1). There were 170 men (55%) and 141 women (45%); 83% of the patients were white, 6% were black, and 11% were of other race. The overall survival rate was 62.1% at 5 years and 45.6% at 10 years. Sufficient clinical data at the time of diagnosis were available to apply the modified Kadish staging system to 261 patients; 50 patients were excluded because of incomplete staging information. A total of 45 patients (17.2%) presented with stage A disease, 130 (49.8%) with stage B disease, 10 (3.8%) with stage C disease, and 76 (29.1%) with stage D disease. The overall mean survival time was 133.4 months (95% confidence interval [CI], 111.0-155.7) in this group of 261 patients. The overall mean survival time for patients with stage A disease was 145.6 months (95% CI, 129.0-162.2), 149.5 months (95% CI, 119.0-180.0) for those with stage B disease, 72.5 months (95% CI, 32.3-112.7) for those with stage C disease, and 53.7 months (95% CI, 27.3-80.0) for those with stage D disease (Table).

Kaplan-Meier analysis demonstrated the overall and disease-specific survival rates at 10 years to be 83.4% and 90%, respectively, for patients with stage A disease; 49% and 68.3% for those with stage B disease; 38.6% and 66.7% for those with stage C disease; and 13.3% and 35.6% for those with stage D disease (Figure 3 and Figure 4). All pairwise log-rank comparisons between stages were statistically significant (P<.01) except for those involving stage C disease (owing to the small size of this subgroup [n=10]).

Lymph node status at the time of diagnosis was available in 130 cases. Of these cases, 112 (86.2%) presented with no lymph node involvement, 16 (12.3%) presented with regional involvement (submental, submandibular, internal jugular, retropharyngeal, cervical [not otherwise specified], and regional [not otherwise specified]), and 2 (1.5%) presented with distant metastases. Survival differed significantly based on the presence of lymph node metastases at the time of diagnosis (log-rank test, P<.01; Figure 4).

Treatment modality data were available for 274 cases, revealing that 73 cases (26.7%) were treated with surgery alone, 26 (9.5%) with radiotherapy alone, 170 (62%) with both surgery and radiotherapy, and 5 (1.8%) with neither treatment. Kaplan-Meier analysis in these groups (Figure 5) demonstrated that the longest duration of mean survival was in patients who received both modalities (216.8 months) (95% CI, 188.6-245.0), fol-
allowed by those who received surgery alone (208.1 months) (95% CI, 155.7-260.6), radiotherapy alone (92.8 months) (95% CI, 64.9-120.8), and neither therapy (53.7 months) (95% CI, 10.0-33.9), but log-rank tests found significance only between the groups receiving radiotherapy alone and those with combined modality treatment (P = .002). Age at diagnosis was examined and found to be significant in univariate analysis (P < .001). Sex (P = .15), race (P = .55), SEER geographic registry (P = .44), and year of diagnosis (P = .89) were not statistically significant prognostic factors. Cox multivariate regression analysis was performed to adjust for interaction between covariates and confirmed that stage remained a significant predictor of disease-specific survival (P < .001). Treatment modality also remained a statistically significant factor in the multivariate model (P < .05).

Laterality data was present for 179 patients, with an even distribution of 48.6% left-sided, 46.4% right-sided, and 5.0% bilateral disease. The most common site of disease was the nasal cavity (n = 212), followed by the ethmoid (n = 43) and accessory (n = 21) sinuses. Cases were drawn from 12 of the possible 13 geographic registries in the SEER database.

The rarity of ENB has made accurate assessment of survival and prognostic strength of various staging systems difficult. The SEER registries collectively provide a population-based database of patients with cancer comparable to the national population with regard to socioeconomic status and education. In addition to allowing analysis of a larger patient cohort, the cohort in this database may also permit a more generalizable description of survival and prognostic factors than cohorts based at specialized tertiary referral centers.

Some of the basic characteristics of our study population, such as the mean age of 53 years and the wide range of patient ages, are in accord with previously published studies. Many authors report means and median peak incidences in patients between the ages of 43.6 and 55.4 years, although others have supported a bimodal peak in incidence around the second and sixth decades of life, with 1 study reporting a mean age of 27 years in a set of 21 patients.7,10,14,15 The results of our study strongly favor a unimodal distribution, with the majority of patients between the ages of 45 and 64 years and only 22 of 301 patients in the 10- to 24-year-old range (Figure 1). This age distribution is in agreement with 2 recent studies that reported unimodal peaks in the fourth and fifth decades of life.3,10

The need for a robust staging system has led to the development of alternatives to the Kadish or modified Kadish systems, and the SEER registry data provide evidence for the superiority of a modified Kadish staging system in predicting survival. Further research is needed to validate these findings in larger patient populations.

Figure 1. Age distribution.

Figure 2. Kaplan-Meier overall survival curve (using modified Kadish stage).
Kadish staging systems. Biller et al15 first proposed a system based on the TNM type of classification in 1990, and Dulguerov et al16 proposed a refined TNM system in 1992. Some of the inadequacies of the Kadish system named by these authors include the inability of the Kadish groupings to effectively stratify patients, with few patients falling into group A and very different types of spread being consolidated in group C. Still, some authors have found acceptable prognostic utility with this staging system.10,17 Indeed, Dias et al18 compared the staging systems of Kadish, Biller, and Dulguerov and colleagues in a group of 35 patients and found that the Kadish system was the only classification that yielded a statistically significant discrimination between stages. Unfortunately, limitations in the detail of site data extracted from the SEER database, such as a lack of specific coding for involvement of the cribriform plate or superior ethmoid cells, prevented the application of these staging systems to our data set and a formal comparison of staging systems.

In a meta-analysis of case series between 1990 and 2000, the overall 5-year survival rate in 26 studies was 45% (SD, 22%), compared with our study’s estimated survival rate of 62.1%.19 The meta-analysis found the 10-year survival rate to be 52% (SD, 27%), which is comparable to our study’s 10-year survival rate of 45.3%. A study of all patients with ENB in Denmark between 1978 and 2000 (N=40) found the overall or crude survival rate at 5 years to be 61%.20 Morita et al19 studied 49 patients and found a 5-year survival rate of 69%. In a review of 97 cases between 1967 and 1977, Elkon et al7 found a favorable 3-year overall survival rate in patients with stage A or B disease (88.9% and 83.3%, respectively), while patients with stage C disease had only a 52.9% survival rate at 3 years. Recently, the University of Virginia Health System updated a series of 50 cases and reported higher disease-free survival rates of 86.5% and 82.6% at 5 and 15 years; all patients received multimodality treatment in-

<table>
<thead>
<tr>
<th>Modified Kadish Stage</th>
<th>Sample Size, No.</th>
<th>Overall Survival, %</th>
<th>Disease-Specific Survival, %</th>
<th>Mean Survival Time, mo (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>45</td>
<td>83.4</td>
<td>90.0</td>
<td>145.6 (129.0-162.2)</td>
</tr>
<tr>
<td>B</td>
<td>130</td>
<td>49.0</td>
<td>68.3</td>
<td>149.5 (119.0-180.0)</td>
</tr>
<tr>
<td>C</td>
<td>10</td>
<td>38.6</td>
<td>66.7</td>
<td>72.5 (32.3-112.7)</td>
</tr>
<tr>
<td>D</td>
<td>76</td>
<td>13.3</td>
<td>35.6</td>
<td>53.7 (27.3-80.0)</td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier disease-specific survival curve (using modified Kadish stage).

Figure 4. Kaplan-Meier curve of disease-specific survival (by lymph node status).

Figure 5. Kaplan-Meier curve of disease-specific survival (by treatment modality: surgery, radiotherapy, or both).
cluding craniofacial resection, radiotherapy, and chemotherapy for stage C disease.\textsuperscript{11}

Cervical lymph node metastases are commonly studied in cases of ENB, as the management of the neck in patients who present without apparent nodal involvement is not clear. The literature reports a 10% to 33% incidence of neck metastasis, which is similar to the 15.2% in our study. Nodal status has been reported to be one of the most important prognostic factors in survival, a finding that is consistent with the clear impact on disease-specific survival that was shown in the present study (Figure 4) (\textit{P}<.001).\textsuperscript{10,18,19} Surgical treatment of ENB now commonly includes craniofacial resection, although no clear consensus for overall management, including radiotherapy and chemotherapy, currently exists. Our data revealed improved survival with multimodality treatment as opposed to radiotherapy alone, which is consistent with previous studies.\textsuperscript{19}

Limitations of this study include the reliance on the SEER data model and its coding system. The modified Kadish stage was derived from available anatomical site data and was not determined by clinical data or radiologic data in the patient record, as in most institutional series. Modified Kadish stage group C included a small number of cases (n=10), limiting the ability to make meaningful comparisons with this subgroup. Also, there may be coding errors in the database, although only 1 grossly incorrect case required exclusion. As with most other studies of ENB, the series of patients covers a large period of time, during which treatment and diagnostic techniques have evolved. Despite these limitations, we were able to evaluate the largest cohort (to our knowledge) of patients with ENB described to date and to provide insight into the utility of the modified Kadish staging system and the clinical behavior of this disease.

In conclusion, we analyzed survival and prognostic characteristics of ENB in the largest cohort of patients reported to date. The modified Kadish staging system is a useful predictor of survival in patients who present with this uncommon tumor. The mean age at diagnosis of ENB has a unimodal peak incidence at 53 years. The results of our study also reinforce the value of lymph node status and treatment modality as predictors of survival.

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Author Contributions: Dr Morris had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Morris. Acquisition of data: Jethanamest. Analysis and interpretation of data: Jethanamest, Morris, and Sikora. Drafting of the manuscript: Jethanamest and Morris. Critical revision of the manuscript for important intellectual content: Morris, Sikora, and Kutler. Statistical analysis: Jethanamest, Morris, and Sikora. Administrative, technical, and material support: Jethanamest. Study supervision: Sikora and Kutler.

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REFERENCES