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Role of surgical treatment for esthesioneuroblastomas: 31-Year experience at a single institution

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ABSTRACT

Objective: This study aimed to re-assess the outcomes of different surgical methods for esthesioneuroblastoma (ENB) in a single institution, with emphasis on changes in surgical treatment with regard to endoscopic approaches in patients with ENB.

Subjects and methods: We retrospectively reviewed the data of 35 patients with ENB treated over the last 31 years.

Results: The 5-year overall and disease-free survival rates were 66.8% and 50.8%, respectively. Disease-free survival in the endoscopic surgery group was significantly higher compared to that of craniofacial surgery group (P = 0.035). In the endoscopic surgery group, nine of 10 patients did not exhibit local failure or regional recurrence over a mean followup period of 64.3 months, which was longer than the mean time to recurrence (22.0 months) observed in this study.

Conclusion: Given its significant survival outcomes and high rate of local control, endoscopic surgery could be preferred as a minimally invasive treatment with potentially low morbidity and possible oncological validity for the treatment of ENB.

1. Introduction

Esthesioneuroblastoma (ENB) is an extremely rare malignant tumor originating in the cribriform plate, superior turbinate, or superior nasal septum. Uncertainty regarding its exact cellular origin has led to the tumor being assigned various names. However, only two terms are used in current publications to indicate this tumor type, namely, ENB and olfactory neuroblastoma. Although there have been no precise epidemiological studies, ENB has been reported to account for 2–6% of sinonasal malignant tumors (Berger et al., 1924; Rimmer et al., 2014). The biological behavior of this tumor ranges from indolent growth, with patients surviving for over 10 years, to highly aggressive growth, characterized by local recurrence, atypical distant metastasis, and less than a few months of survival (Levine et al., 1999; Dulguerov et al., 2001; Constantinidis et al., 2004). Because of their rarity of occurrence, a universally accepted staging system for these tumors is unavailable, leading to several opinions regarding their origin, diagnosis, management, and treatment outcomes.

Based on the findings of a limited number of studies, the gold standard for treatment of ENB is craniofacial resection (CFR) followed by adjuvant radiotherapy and/or chemotherapy (Lund et al., 2003; Smee et al., 2011). However, CFR has serious limitations in terms of high rates of recurrence (locoregional as well as long-range metastasis) and postoperative complications, including cerebrospinal fluid (CSF) leakage, frontal abscess, pneumocephalus, hydrocephalus, intracranial hemorrhage, extended hospital stay, and cosmetic issues. In recent times, the endonasal approach using an endoscope has been used as a universal surgical route, as an alternative to the open transfacial approach (Casiano et al., 2001; Devaiah et al., 2003). Furthermore, because of the recent advances in endoscopic techniques and instruments, such as the use of image-guided surgery (IGS) (Benoit et al., 2009; Ramakrishnan et al., 2013; Al-Qudah, 2015), a purely endoscopic approach, without the transcranial approach, has been attempted for tumor resection in the anterior skull base.

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Data regarding the initial part of the present study were published in 2007 (Kim et al., 2008). The objective of this study was to re-assess the outcomes of different surgical methods among patients diagnosed with ENB at a single institution over a 31-year period, with emphasis on changes in surgical treatment with regard to endoscopic approaches.

2. Materials and methods

2.1. Data collection

Participants were selected upon reviewing the medical records of patients diagnosed with ENB at the Severance Hospital, Seoul, Korea, between January 1985 and December 2015. This study was approved by the institutional review board (No. 2016-0879-001) of the Yonsei University College of Medicine, Seoul, Korea, which waived the need for informed patient consent. The eligibility criteria for this study were histologically verified diagnosis of ENB, treatment received entirely at our institution, and ongoing follow-up. Finally, 35 patients who had completed evaluation at our institution were enrolled in this study. The following details were collected from the medical records: sex, age, major symptoms, subsite of origin, type of initial treatment, postoperative resection margin, tumor recurrence, salvage therapy, and final disease status. Imaging studies, including computed tomography and magnetic resonance imaging, were performed to evaluate the extent of primary disease as well as treatment response. Staging was retrospectively performed according to the modified Kadish system (Kadish et al., 1976; Morita et al., 1993) (Table 1). The Hyams grading system for pathological assessment was not consistently used over the period of the study.

2.2. Treatment modalities

Surgical treatment, either by CFR or by endoscopic surgery, was administered with curative intent. CFR involved standard bifrontal craniotomy with a lateral rhinotomy incision and was performed as a combined skull base/neurosurgical procedure with orbital exenteration included if the extent of spread of malignancy dictated that the malignancy be appropriated on the basis of the findings of initial and subsequent investigations. From 2012 onwards, endoscopic surgery at our institution was assisted by a navigation system (IGS; Medtronic Fusion Guidance System, Louisville, CO). Neck management, including radical neck dissection, was performed only in patients with cervical lymph node metastasis at initial diagnosis. The main chemotherapy regimen with or without radiotherapy was administered over two to six courses every 3 weeks and included etoposide, cisplatin, and ifosfamide. An 8-year-old patient was treated with cyclophosphamide, doxorubicin, and vincristine. Radiotherapy was typically initiated 4–6 weeks after the previous treatment, irrespective of whether it was chemotherapy or surgery. Radiotherapy dosage varied depending on the primary treatment. The median doses of radiotherapy were 5820 cGy (range, 4500–6800 cGy) for primary lesions and 4800 cGy (range, 4500–5000 cGy) for cervical lesions.

2.3. Outcome measures and statistical methods

The mean follow-up period was calculated from the day after completion of primary treatment. Time until first recurrence was defined as the interval between the dates of initial treatment and discovery of recurrence. Local control was defined as the absence of clinical, radiological, or pathological evidence of persistence or recurrence within the original tumor bed following therapy. Survival analyses included the data of patients who died of causes unrelated to the tumor.

Data analyses were performed by Kaplan–Meier time-to-event analysis, log-rank test, and Cox regression analysis. The level of statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Clinical characteristics

The clinical and demographic data of the patients are summarized in Table 2. The study sample included 21 (60.0%) male and 14 (40.0%) female patients. Patient age exhibited unimodal distribution, with the mean age being 46.3 years (range, 8–71 years). The differences in survival among patients based on age and sex were insignificant. The mean follow-up period was 83.5 months (range, 2–360 months).

Distribution of tumors according to the modified Kadish staging system revealed 1 stage A tumor (2.9%), 8 stage B tumors (22.8%), 18 stage C tumors (51.4%), and 8 stage D tumors (22.8%) (Table 3).

Although 17 patients (48.6%) presented no evidence of disease, 3 (8.6%) exhibited recurrent disease, 14 (40.0%) had died of disease, and 1 (2.8%) had died of other causes.

The overall survival (OS) rates at 5 and 10 years after primary treatment were 66.8% and 48.3%, respectively. Disease-free survival (DFS) at 5 years after primary treatment was 52.8%. The OS and DFS of patients were separately evaluated according to the modified Kadish stage of tumors (A/B vs. C/D) by binary analysis. Although the 5-year OS and DFS of patients with more advanced tumors were lower compared to those of patients with early-stage tumors, the differences were not statistically significant. The mean 5-year OS of patients with Kadish A/B or Kadish C/D tumors were 80.0% and 62.6%, respectively. The mean 5-year DFS of patients with Kadish A/B tumors (88.9%) was higher compared to that of patients with Kadish C/D tumors (40.5%). Although only 5 (14.3%) patients exhibited cervical lymph node metastases at initial presentation, this number increased to 12 (34.3%) over the course of the study because of patients with newly developed neck metastasis. The 5- and 10-year OS of patients without cervical lymph node metastases (72.5% and 54.4%, respectively) were higher compared to those of patients with cervical lymph node metastases (58.3% and 27.8%, respectively).

3.2. Primary treatment outcomes

The therapeutic approach was determined upon consideration of age, stage of tumor, and general condition of the patient. As the primary treatment modality, 6 patients (17.1%) were treated

Table 1
Staging system of esthesioneuroblastoma proposed by Kadish et al. and modified by Morita et al. (Kadish et al., 1976; Morita et al., 1993).

Stage	Tumor localization
A	Tumor confined to the nasal cavity
B	Tumor confined to the nasal cavity and paranasal sinuses
C	Tumor extending beyond the nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of the skull, orbit, or intracranial cavity
D	Tumor with metastasis to cervical lymph nodes or distant metastasis