

# Esthesioneuroblastoma

## Continued Follow-up of a Single Institution's Experience

Andrew H. Loy, FRCS; James F. Reibel, MD; Paul W. Read, MD; Christopher Y. Thomas, MD; Steven A. Newman, MD; John A. Jane, MD; Paul A. Levine, MD

**Objectives:** To analyze outcomes and to provide follow-up for our increasing patient cohort with esthesioneuroblastoma.

**Design:** Retrospective cohort analysis.

**Setting:** Patients were examined from September 1, 1976, to May 30, 2004, in a tertiary care academic hospital.

**Patients:** Fifty consecutive patients diagnosed as having esthesioneuroblastoma were treated with a standardized protocol during a 28-year period. Patients with tumors staged Kadish A or B received preoperative radiotherapy followed by craniofacial resection, while patients with Kadish stage C disease were treated with preoperative sequential chemotherapy and radiotherapy followed by a craniofacial resection. The mean follow-up is 93 months (range, 1-330 months).

**Results:** The disease-free survival was 86.5% and 82.6% at 5 and 15 years, respectively. There were 17 patients (34%) who developed recurrent disease, most of which was locoregional (12 patients [71%]). There was a long interval to relapse (mean, 6 years), with the longest time to regional recurrence being 10 years. Distant relapses occurred sooner, with poorer outcomes. Of these 17 patients, 7 (41%) underwent successful salvage surgery, while 3 remain alive with disease.

**Conclusions:** Excellent outcomes for esthesioneuroblastoma are achievable. Long-term follow-up is necessary because of the extended interval for recurrent disease; unlike most sinonasal malignancies, surgical salvage is possible.

*Arch Otolaryngol Head Neck Surg.* 2006;132:134-138

**E**STHESIONEUROBLASTOMA IS an uncommon neoplasm of the nasal cavity, constituting 3% of all endonasal tumors. Since it was first described by Berger and Luc<sup>1</sup> in 1924, only approximately 1000 cases of esthesioneuroblastoma have been reported in the world's literature.<sup>2</sup> The optimal treatment modality for esthesioneuroblastoma continues to be debated because of reports with a limited cohort size and treatment inconsistencies for this rare tumor. Surgery and radiotherapy (RT) are still used by some institutions as single modalities despite the lack of support for single-modality treatment regimens,<sup>3,4</sup> while many other institutions favor surgery followed by RT.<sup>5-8</sup> The use of combined modality treatment with surgery, RT, and chemotherapy in various combinations has been increasingly adopted over the past few years.<sup>9,10</sup> Often, even within the same institution, different treatment modalities may be used, reducing the

power of analysis for this already small group of patients. We have consistently applied a standardized treatment protocol for esthesioneuroblastoma at our institution over the past 28 years. We have also shown that monitoring beyond the standard 5-year period is necessary.<sup>11</sup> This article continues to evaluate and report the results of this standardized protocol with significant long-term follow-up and shows that excellent cure rates are possible for this unusual tumor.

### METHODS

The clinical records of all patients diagnosed as having esthesioneuroblastoma at the University of Virginia Health System from September 1, 1976, to May 30, 2004, were retrospectively reviewed. We focused on the analysis of patients who were diagnosed as having the tumor after 1976, because this marked the year when standardized treatment for this group of patients was implemented at our institution.<sup>12,13</sup> The patient population was obtained

**Author Affiliations:**  
Departments of Otolaryngology-Head and Neck Surgery (Drs Loy, Reibel, and Levine), Radiation Oncology (Dr Read), Internal Medicine (Dr Thomas), Ophthalmology (Dr Newman), and Neurological Surgery (Dr Jane), University of Virginia Health System, Charlottesville. Dr Loy is now with the Department of Otorhinolaryngology, Tan Tock Seng Hospital, Singapore.

from a tumor database maintained by the Department of Otolaryngology–Head and Neck Surgery. Institutional review board approval was obtained before the initiation of the study.

All patients included in the study were cared for by a multidisciplinary team consisting of otolaryngologists–head and neck surgeons, radiation and medical oncologists, neurosurgeons, neuroradiologists, and neuro-ophthalmologists. Computed tomography and, later in the series, magnetic resonance imaging were used to assess the full extent of each tumor before commencement of treatment. The patients' tumors were staged based on the clinical and radiologic presentation according to the Kadish classification. Kadish stage A refers to disease confined to the nasal cavity; stage B, disease confined to the nasal cavity and 1 or more paranasal sinuses; and stage C, disease extending beyond the nasal cavity or paranasal sinuses and including involvement of the orbit, base of the skull, or intracranial extension and cervical metastatic disease or distant metastatic sites.<sup>14</sup>

## TREATMENT

Patients whose disease was Kadish stage A or B esthesioneuroblastoma received preoperative RT to 5000 cGy, followed by a craniofacial resection that was performed in combination with the neurosurgical team 4 to 6 weeks after the completion of RT.

Patients with Kadish stage C disease were treated with preoperative sequential chemotherapy and RT followed by craniofacial resection. The chemotherapy regimen initially consisted of cyclophosphamide and vincristine sulfate, with the addition of doxorubicin in a selected group of patients. Patients who had a good response to the chemotherapy would receive a second cycle of chemotherapy. All but 2 patients with Kadish stage C esthesioneuroblastoma received neoadjuvant chemotherapy. Craniofacial resection was performed by the surgical teams, with technical details as highlighted in previous reports.<sup>12,15-17</sup>

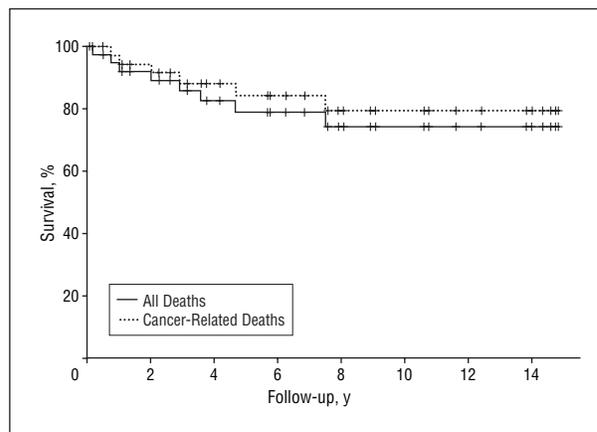
## STATISTICAL ANALYSIS

The Kaplan-Meier method was used to estimate the probability of recurrence or death. Death caused by the disease was treated as an end point for disease-specific survival, while other deaths, such as postoperative deaths, were treated as censored observations. The subsequent period was defined as time from surgery to time of last follow-up or death, or recurrence when the studied event was a recurrence.

## RESULTS

Between September 1, 1976, and May 30, 2004, 60 consecutive patients with esthesioneuroblastoma were examined at our institution. Ten patients were excluded from this analysis because either they did not receive complete treatment at our institution or the surgical procedures were palliative. The remaining 50 patients received our standardized treatment protocol and formed the basis of this study. The pathological results were reviewed at the University of Virginia Health System and confirmed as esthesioneuroblastoma in all patients. The patients with sinonasal undifferentiated carcinoma, which may be confused with Hyams grade 4 esthesioneuroblastoma, were excluded from this analysis.<sup>18-20</sup>

The demographics are as follows. The patients ranged in age from 9 to 77 years (mean age, 43.6 years), with



**Figure.** Disease-free survival rate (Kaplan-Meier survival curve) for esthesioneuroblastoma for the 50 patients in this study.

26 males and 24 females. The number of patients was greatest in the fourth to sixth decades of life.

Most of the 50 patients presented with nasal symptoms of obstruction (38 [76%]) and epistaxis (21 [42%]). Eye symptoms of visual disturbance (5 patients [10%]) and exophthalmos (4 patients [8%]) were also present. Other symptoms included headache in 15 patients (30%), nasal polyp in 8 (16%), epiphora in 3 (6%), and cervical metastases in 3 (6%).

The extent of tumor was noted on imaging to involve the maxillary sinus in 14 patients (28%), the sphenoid sinus in 7 (14%), the frontal sinus in 4 (8%), erosion of the cribriform plate in 21 (42%), the intracranial area in 12 (24%), and the pterygopalatine fossa in 1 (2%). Orbital invasion was noted in 19 patients (38%).

The tumors were Kadish stage A in 4 patients (8%), stage B in 14 (28%), and stage C in 32 (64%). As previously stated, the patients with Kadish stages A and B disease received preoperative RT followed by planned craniofacial resection 4 to 6 weeks later, while those with Kadish stage C disease received neoadjuvant sequential chemotherapy and RT followed by craniofacial resection. The mean follow-up is 93 months (7.8 years), with a range of 1 to 330 months.

There are 7 patients (14%) who have died of disease, while 2 (4%) have died of unrelated causes. The disease-free survival was 86.5% and 82.6% at 5 and 15 years, respectively (**Figure**).

There were 17 patients (34%) who developed recurrent disease, most of which was locoregional (12 patients [71%]) (**Table 1**). There was a long interval to relapse (mean, 6 years), with the longest time to regional recurrence being 10 years. Distant relapses occurred sooner, with poorer outcomes (3 of 5 are dead of disease). Most distant metastases were in the bone. Of these 17 patients, 7 (41%) underwent successful salvage surgery and remain free of tumor, while 3 (18%) remain alive with disease.

Despite using RT and chemotherapy before craniofacial resection, we did not experience significantly higher complication rates compared with other series (**Table 2**), consistent with prior findings.<sup>12</sup> There were 10 patients with postoperative neurological complications. Five patients had cerebrospinal fluid leaks, 4 of which were

**Table 1. Recurrent Disease**

Patient No.	Location	Treatment	Status
<b>Local Recurrences</b>			
1	Sphenoid sinus and clivus	Chemotherapy	Salvaged
2	L frontal lobe	Craniotomy plus chemotherapy	Salvaged
3	R orbit and cavernous sinus	Surgery plus chemotherapy	DOD
4	Anterior cranial fossa	Chemotherapy	DOD
<b>Regional Recurrences</b>			
5	Level 2 nodes	RT	Salvaged
6	Parotid node	Parotidectomy	Salvaged
7	Level 2 node Level 5 node Parotid node	R MRND RT Parotidectomy	AWD
8	Bilateral nodes	Bilateral ND	AWD
9	Retropharyngeal node	Excision plus chemotherapy	AWD
10	Level 1 node	R MRND	DOD
11	R jugular foramen	Chemotherapy	DOD
12	Level 5 node	No treatment	DOD
13	R side of the neck	R RND plus RT	Salvaged
14	Bilateral neck nodes	Bilateral MRND plus RT	Salvaged
15	R side of the neck	R MRND plus RT	AWD
<b>Distant Recurrences</b>			
16	Lumbar spine	RT	DOD
17	L humerus	Chemotherapy plus RT	Salvaged
18	Diffuse bone metastases	Chemotherapy	DOD
19	R hilar nodes	Chemotherapy	DOD
20	Liver metastases	Chemotherapy	AWD

Abbreviations: AWD, alive with disease; DOD, dead of disease; L, left; MRND, modified radical neck dissection; R, right; RT, radiotherapy.

treated conservatively with lumbar peritoneal drains and 1 of which required no therapy. None of the patients in this series, since 1997, have had a postoperative cerebrospinal fluid leak as a complication of surgery, which we attribute to improving surgical expertise and coordination between the teams of neurosurgeons and head and neck surgeons. We also believe that the creation of a watertight seal to separate the intracranial contents and the nasal cavity with the use of a fat-fascia graft together with fibrin glue has a positive effect, although we did not find a statistical correlation on analysis. There was 1 patient with elevated intracranial pressure, 3 patients with pneumocephalus who were treated with surgical decompression, and 1 patient with stroke syndrome that caused temporary left hemiplegia that completely resolved. There were no cases of meningitis, and this again emphasizes the value of achieving a watertight seal. Complications resulting from chemotherapy were few (5 [17%] of 30 patients), with only 2 major complications (acute myocardial infarction and bilateral vocal cord palsy). There was 1 patient with peripheral neuropathy, 1 with digital paraesthesia, and 1 who developed herpes zoster during his treatment. Complications related to RT included orbital problems of cataracts in 2 patients and keratopathy in 1 patient. Of the 50 patients, 8 developed systemic complications that were not life threatening. Of

**Table 2. Complications of Treatment for Esthesioneuroblastoma in the 50 Patients**

Category	No. (%) of Patients	Complications
CNS	10 (20)	1 Increased ICP, 3 pneumocephalus, 1 transient stroke syndrome, and 5 CSF leaks
Orbital	9 (18)	3 Epiphora, 2 radiation-induced cataracts, 1 radiation keratopathy, 2 transient fourth cranial nerve palsy, and 1 periorbital cellulitis
Systemic	8 (16)	1 Hyponatremia, 1 temporary respiratory arrest, 2 abdominal wound seroma, 2 DI, 1 pulmonary embolus, and 1 hypothyroidism
Chemotoxic	5 (10)	1 Acute myocardial infarction, 1 bilateral vocal cord palsy, 1 peripheral neuropathy, 1 herpes zoster, and 1 digit paraesthesia
Infectious	3 (6)	2 Infected bone flaps and 1 epidural abscess

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DI, diabetes insipidus; ICP, intracranial pressure.

these 8 patients, 1 had hyponatremia; 1 experienced respiratory arrest, from which he fully recovered; 2 had an abdominal wound seroma from the fat-fascia graft harvest site; 2 had diabetes insipidus; 1 had a pulmonary embolism that was treated by anticoagulation; and 1 had hypothyroidism. The infectious complications were few (3 [6%] of 50 patients), with 2 patients having infected bone flaps that required removal and 1 having an epidural abscess that was surgically drained.

## COMMENT

This series represents many patients with esthesioneuroblastoma who have been treated at a single institution using a standardized protocol with an extended follow-up. Since the publication of previous results with 35 patients,<sup>11</sup> we have continued to evaluate our results and show that long-term effective control can be achieved when neoadjuvant therapy is combined with aggressive surgical resection. Most of our patients (64%) presented with advanced Kadish stage C disease.

In a recent review of 945 patients by Broich et al,<sup>2</sup> the Kadish classification was applied retrospectively, revealing that 18% of the patients had stage A, 32% had stage B, and 49% had stage C disease. Of the patients with a minimum 5-year follow-up, survival rates for combined therapy, surgery, and RT were 72.5%, 62.5%, and 53.8%, respectively. Dulguerov et al<sup>21</sup> more recently performed a meta-analysis of publications between 1990 and 2000, detailing treatment of esthesioneuroblastoma. The treatment modalities analyzed were surgery alone; surgery and RT; RT alone; a combination of surgery, RT, and chemotherapy; RT and chemotherapy; and chemotherapy alone. Statistical analysis compared the different treatment modalities against the approach with the highest average survival (surgery and RT). They identified 26 studies that described 390 patients with esthesioneuroblastoma. Overall survival at 5 years was 41%, with data extracted from 24

publications. They found that the combination of surgery and RT was the most frequently used treatment (44%) and was associated with the best average survival results (65%). Survival results were 48% for surgery alone, 37% for RT alone, 40% for chemotherapy alone, and 51% for RT plus chemotherapy. They concluded that combination surgery and RT seemed to be the optimal approach to treatment, with single-modality treatment being reserved only for a patient with a small tumor located well below the cribriform plate. Even then, postoperative RT seems justified in almost all patients to keep the risk of local recurrence to a minimum.<sup>21</sup>

While the use of chemotherapy has been arbitrary in most institutions, we have consistently treated patients with Kadish stage C disease with chemotherapy as part of our multimodality protocol. Our philosophy is based on the principle that these tumors share certain biological characteristics with other chemosensitive tumors of neural crest origin (neuroblastomas, high-grade neuroendocrine carcinomas, and primitive neuroectodermal tumors).<sup>22</sup> Esthesioneuroblastomas are chemosensitive tumors, and our preoperative regimen includes cyclophosphamide, 650 mg/m<sup>2</sup>; and vincristine, 1.5 mg/m<sup>2</sup>, with a maximum dose of 2 mg. Our cohort tolerated the chemotherapy well, with few adverse effects, the most significant being a patient who sustained an acute myocardial infarction and another who developed bilateral vocal cord palsy, necessitating a tracheotomy. With a mean extended follow-up of 7.8 years, we have demonstrated a disease-free survival of 86.5% and 82.6% at 5 and 15 years, respectively.

Late relapse is a particular feature in patients with esthesioneuroblastoma.<sup>6,23</sup> In this series, local recurrence developed in 4 patients a mean of 72 months following definitive treatment. The first patient with stage C disease developed recurrence in the sphenoid sinus and clivus 7 months after initial treatment, but was successfully treated with salvage chemotherapy, while the second developed recurrence in the left frontal lobe 155 months after initial treatment and again was successfully treated with salvage surgery and chemotherapy. The remaining 2 patients developed recurrences in the orbit/cavernous sinus and anterior cranial fossa, respectively, and have died of disease. Of the 8 patients in whom delayed cervical metastases developed, the mean time of recurrence following definitive treatment was 76.8 months. There were 4 patients who sustained 2 to 4 episodes of cervical recurrences, despite surgical and adjuvant therapeutic intervention. In this group with cervical recurrences, 4 (50%) of 8 patients were successfully treated with salvage neck dissection and adjuvant RT, while 2 remain alive with disease. There were 5 patients who developed distant metastases following definitive treatment, and these patients had a shorter mean time to recurrence (only 13.4 months). The outcome is generally poor in this group of patients, with 3 of 5 having died of disease and 1 remaining alive with tumor despite adjuvant treatment. Despite the patients with distant recurrences, we continue to recommend that aggressive salvage therapy be undertaken because this can be beneficial as either extended palliation or extended survival.

The role of elective neck treatment for esthesioneuroblastoma remains controversial. The incidence of cervi-

cal metastases in recent publications<sup>24,25</sup> has ranged from 17% to 33%. Furthermore, the presence of palpable lymph nodes at presentation has been a poor prognostic factor for survival (eg, the 5-year survival was 0% in patients in whom nodes were present and 65% in those in whom they were absent).<sup>10</sup> This has prompted several researchers to propose that elective nodal treatment, mainly in the form of RT, be considered in selected patients. In our series, the number of patients who ultimately developed neck node disease was 10 (20%). In their series of 22 patients with esthesioneuroblastoma who received RT at the University of Florida, Monroe et al<sup>25</sup> performed elective neck RT in 11 of 20 patients; 2 patients had cervical metastases at presentation for RT. They found that cervical metastases ultimately occurred in 6 (27%) of the 22 patients. No neck recurrences occurred in the 11 patients treated with elective neck RT, compared with 4 neck recurrences (44%) in the 9 patients not receiving elective irradiation. They suggest that there is a higher cervical failure rate than previously recognized and that elective neck RT should be considered in the routine treatment of esthesioneuroblastoma. We did not routinely treat the necks electively in our patient cohort to avoid additional morbidity to the patient who is already undergoing craniofacial resection, and have performed salvage neck dissections in those who subsequently developed cervical recurrences.

Several series have focused recently on the role of endoscopic resection for esthesioneuroblastoma. Initial reports<sup>26,27</sup> recommended the use of endoscopic surgery followed by stereotactic radiosurgical  $\gamma$  knife therapy. Casiano et al<sup>28</sup> described a series of 5 patients with Kadish stage A or B esthesioneuroblastoma who underwent endoscopic resection and immediate reconstruction of the anterior skull base. Their study included primary and secondary salvage treatment, and all patients were treated with adjuvant external beam RT. They showed no local recurrence, with a mean follow-up of only 31 months. A recent series<sup>29</sup> had 7 patients with esthesioneuroblastoma who underwent endoscopic excision of the nasal and sinus components, together with anterior craniotomy for the removal of the cribriform plate or anterior cranial fossa tumor extension. All patients received adjuvant RT and, with a mean follow-up of 62.3 months, 2 of the 7 patients had recurrences. We believe that craniofacial resection still remains the gold standard by which all other treatments need to be judged, in conjunction with an appropriate follow-up; craniofacial resection should be the standard of care for all patients with esthesioneuroblastoma.

In conclusion, excellent outcomes for esthesioneuroblastoma are achievable with multimodality treatment. Long-term follow-up of these patients is necessary because of the extended interval for recurrent disease, and unlike most sinonasal malignancies, surgical salvage is possible, with good outcomes.

**Submitted for Publication:** May 9, 2005; final revision received October 13, 2005; accepted October 27, 2005.  
**Correspondence:** Paul A. Levine, MD, Department of Otolaryngology–Head and Neck Surgery, University of Virginia Health System, PO Box 800713, Charlottesville, VA 22908-0713 (pal@virginia.edu).

**Financial Disclosure:** None.

**Disclaimer:** Dr Levine was not involved in the editorial evaluation or decision to accept this article for publication.

**Previous Presentation:** This study was presented at the Sixth International Conference on Head and Neck Cancer; August 10, 2004; Washington, DC.

## REFERENCES

- Berger L, Luc R. L'esthesioneuroepitheliome olfactif. *Bull Cancer (Paris)*. 1924; 13:410-421.
- Broich G, Pagliari A, Ottaviani F. Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924. *Anticancer Res*. 1997; 17:2683-2706.
- Rinaldo A, Ferlito A, Shaha AR, et al. Esthesioneuroblastoma and cervical lymph node metastases: clinical and therapeutic implications. *Acta Otolaryngol*. 2002; 122:215-221.
- Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: surgical treatment without radiation. *Laryngoscope*. 1990;100:1199-1201.
- Resto VA, Eisele DW, Forastiere A, et al. Esthesioneuroblastoma: the Johns Hopkins experience. *Head Neck*. 2000;22:550-558.
- Chao KS, Kaplan C, Simpson JR, et al. Esthesioneuroblastoma: the impact of treatment modality. *Head Neck*. 2001;23:749-757.
- Irish J, Dasgupta R, Freeman J, Gullane P, Gentili F, Brown D. Outcome and analysis of the surgical management of esthesioneuroblastoma. *J Otolaryngol*. 1997; 26:1-7.
- Constantinidis J, Steinhart H, Koch M, et al. Olfactory neuroblastoma: the University of Erlangen-Nuremberg experience 1975-2000. *Otolaryngol Head Neck Surg*. 2004;130:567-574.
- McElroy EA Jr, Buckner JC, Lewis JE. Chemotherapy for advanced esthesioneuroblastoma: the Mayo Clinic experience. *Neurosurgery*. 1998;42:1023-1027.
- Koka VN, Julieron M, Bourhis J, et al. Aesthesioneuroblastoma. *J Laryngol Otol*. 1998;112:628-633.
- Levine PA, Gallagher R, Cantrell RW. Esthesioneuroblastoma: reflections of a 21-year experience. *Laryngoscope*. 1999;109:1539-1543.
- Levine PA, McLean WC, Cantrell RW. Esthesioneuroblastoma: the University of Virginia experience 1960-1985. *Laryngoscope*. 1986;96:742-746.
- Levine PA, Debo RF, Meredith SD, Jane JA, Constable WC, Cantrell RW. Craniofacial resection at the University of Virginia (1976-1992): survival analysis. *Head Neck*. 1994;16:574-577.
- Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma: a clinical analysis of 17 cases. *Cancer*. 1976;37:1571-1576.
- Levine PA, Scher RL, Jane JA, et al. The craniofacial resection: eleven-year experience at the University of Virginia: problems and solutions. *Otolaryngol Head Neck Surg*. 1989;101:665-669.
- Perry C, Levine PA, Williamson BR, Cantrell RW. Preservation of the eye in paranasal sinus cancer surgery. *Arch Otolaryngol Head Neck Surg*. 1988;114: 632-634.
- McCary WS, Levine PA, Cantrell RW. Preservation of the eye in the treatment of sinonasal malignant neoplasms with orbital involvement. *Arch Otolaryngol Head Neck Surg*. 1996;122:657-659.
- Hyams VJ. Tumors of the upper respiratory tract and ear. In: Hyams VJ, Batsakis JG, Michaels L, eds. *Atlas of Tumor Pathology*. Washington, DC: Air Force Institute of Pathology; 1988:240-248. Second series, Fascicle 25.
- Frierson HF Jr, Mills SE, Fechner RE, Taxy JB, Levine P. Sinonasal undifferentiated carcinoma: an aggressive neoplasm derived from schneiderian epithelium and distinct from olfactory neuroblastoma. *Am J Surg Pathol*. 1986;10: 771-779.
- Levine PA, Frierson HF, Mill SE, Stewart FM, Fechner RE, Cantrell RW. Sinonasal undifferentiated carcinoma: a distinct and highly aggressive neoplasm. *Laryngoscope*. 1987;97:905-908.
- Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol*. 2001;2:683-690.
- Bhattacharyya N, Thornton AF, Joseph MP, Goodman ML, Amrein PC. Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation: results in 9 cases. *Arch Otolaryngol Head Neck Surg*. 1997;123:34-40.
- Argiris A, Dutra J, Tseke P, Haines K. Esthesioneuroblastoma: the Northwestern University experience. *Laryngoscope*. 2003;113:155-160.
- Davis RE, Weissler MC. Esthesioneuroblastoma and neck metastasis. *Head Neck*. 1992;14:477-482.
- Monroe AT, Hinerman RW, Amdur RJ, et al. Radiation therapy for esthesioneuroblastoma: a rationale for elective neck irradiation. *Head Neck*. 2003;25: 529-534.
- Unger F, Walch C, Stammberger H, Papaefthymiou G, Haselsberger K, Pendl G. Olfactory neuroblastoma (esthesioneuroblastoma): report of six cases treated by a novel combination of endoscopic surgery and radiosurgery. *Minim Invasive Neurosurg*. 2001;44:79-84.
- Walch C, Stammberger H, Anderhuber W, et al. The minimally invasive approach to olfactory neuroblastoma: combined endoscopic and stereotactic treatment. *Laryngoscope*. 2000;110:635-640.
- Casiano RR, Numa WA, Falquez AM. Endoscopic resection of esthesioneuroblastoma. *Am J Rhinol*. 2001;15:271-279.
- Devaiah AK, Larsen C, Tawfik O, O'Boynick P, Hoover LA. Esthesioneuroblastoma: endoscopic nasal and anterior craniotomy resection. *Laryngoscope*. 2003; 113:2086-2090.