Changing Trends in the Management of Esthesioneuroblastoma: Irish and International Perspectives

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Abstract

Objectives Evaluation of the changing trends in esthesioneuroblastoma in an Irish context and review of management options nationally to clarify the best current therapeutic approach by comparing with international research on this uncommon malignancy.

Design Retrospective review.

Setting Tertiary referral center.

Participants All patients presenting with esthesioneuroblastoma in Beaumont hospital or on the National Cancer Registry of Ireland between 1994 and 2013.

Main Outcome Measures Recurrence-free and overall survival.

Results During the study period, 32 cases of esthesioneuroblastoma were diagnosed (0.4 per million per year). Average age at diagnosis was 57 years; however, two cases were under 20. The majority (62.5%) were male. Patients predominantly presented with epistaxis or nasal congestion (73%), while two cases were identified incidentally on radiological investigations. Twenty-seven cases underwent primary surgical management (two post neo-adjuvant treatment) with seventeen requiring bifrontal craniotomy. Twenty-four of these received postoperative radiation therapy. Overall, 5-year survival was 65%. Kadish A/B patients exhibited 100% 5-year disease-specific survival versus 54% in Kadish C/D ($p = 0.011$). Hyams grade I/II patients exhibited 75% 5-year disease-specific survival versus 63% in Hyams grade III/IV ($p = 0.005$). Patients treated endoscopically exhibited 100% 5-year disease-specific survival versus 51% in those treated via an open approach ($p = 0.102$).

Conclusions Many controversies exist in the diagnosis and management of this condition. Despite this, results from Irish data are mostly concordant with the international literature. The rising incidence of this disease may represent improved pathological recognition. An increasing number of esthesioneuroblastoma cases are being successfully treated via endoscopic surgery.

Keywords

- esthesioneuroblastoma
- sinonasal malignancy
- olfactory neuroblastoma
- skull base

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Introduction

Esthesioneuroblastoma is a primitive neuroectodermal malignant neoplasm that arises from olfactory epithelial cells of the upper nasal cavity. First described by Berger et al in 1924,¹ it is an uncommon tumor with a reported incidence of 4 per 10 million people per year,² with only ~1,400 cases described in the literature.³ It accounts for 3 to 5% of tumors in the sinonasal tract.^{4,5} Although it presents at a wide range of ages, and traditionally was described as having a bimodal distribution with peaks in the second and sixth decades,⁴ recent studies would suggest the peak in the second decade to be much smaller than previously believed and that there may be an even distribution across decades, with peaks in the fifth and sixth decade.^{3,6,7} There is slight male predominance with a reported ratio of ~55:45 male:female, based on large cohort studies and the Surveillance, Epidemiology, and End Results (SEER) database,^{5,6,8} although other studies have reported no gender differences in incidence.⁹

Esthesioneuroblastoma is of neural crest origin with molecular analysis suggesting it is derived from immature olfactory neurons.¹⁰ Although under debate, the most likely and generally accepted site of origin is the region of the basal cells of the olfactory neuroepithelium.¹¹ It is a small round blue cell tumor, which is phenotypically intermediate between a pure neural neoplasm and a neuroendocrine epithelial tumor.⁷ Irregular nests of small round hyperchromatic cells forming lobules or diffuse sheets within fibrovascular stroma and displaying varying degrees of rosettes and pseudorosettes are characteristic histologic features of esthesioneuroblastoma.¹²

The lack of randomized controlled trials has hindered the establishment of a gold standard treatment protocol for esthesioneuroblastoma. Current best practice in management is based largely on retrospective observational studies, which typically have limited numbers of patients due to the rarity of this disease. Nonetheless, observational studies generally indicate that surgery combined with postoperative radiation results in prolonged disease-free and overall survival compared with either treatment modality alone.

Traditional approach to surgical management of esthesioneuroblastoma has involved anterior craniofacial resection through a combined bifrontal craniotomy and transfacial approach to ensure en bloc removal including anterior skull base resection. However, there remains a high postoperative morbidity of 35% and mortality of 2 to 5%.¹³ Therefore, other approaches, including a transnasal, transfacial approach via a lateral rhinotomy incision, have been described with reduced morbidity and outcomes comparable to traditional anterior craniofacial resection.¹⁴ More recently, expansion of endoscopic endonasal techniques has facilitated treatment of anterior skull base malignancies via minimally invasive approaches, but respecting oncologic principles.¹⁵ Treatment of esthesioneuroblastoma by this method was first attempted by Stammberger et al,¹⁶ with further studies establishing that the endoscopic approach is an appropriate treatment modality in carefully selected patients.^{7,17,18}

Esthesioneuroblastoma has a long natural history characterized by high rates of locoregional recurrence after conven-

tional therapy; therefore, close post-treatment surveillance is advised.¹⁹ Due to the complexity in the diagnosis and treatment of this tumor and the debate that exists on the best practice, management in a tertiary referral center involving a widely skilled multidisciplinary team is appropriate.

Methods

National data were gathered from patients on the National Cancer Registry Ireland (NCRI) database between 1994 and 2013 and through retrospective chart review of patients managed through Beaumont hospital in the period with any histopathologically newly diagnosed cases of esthesioneuroblastoma. Data from Northern Ireland were not included in the study because that would be included in the Northern Ireland Cancer Registry as it is a part of the United Kingdom. This study was approved by the Beaumont Medical Research Ethics Committee. Data on Hyams grade, Kadish stage, TNM stage, management (surgery/radiation/chemotherapy), recurrence, and survival were gathered and analyzed.

A choropleth map, or visually graded representation of frequency or density within predefined areas, was generated to depict number of cases by county of origin within Ireland. This was generated using CartoDB® software (CartoDB, Madrid). Statistical analysis was performed using IBM SPSS Statistics Version 23.0.0.2 software (IBM Corp., New York, United States). For each patient, the disease-specific survival was measured in days from the date of diagnosis to censoring (either the date of the latest follow-up or the date of death by other cause) or death from disease, whichever occurred first. Recurrence-free survival was measured in the same way, but considering date of diagnosis of recurrence instead of death from disease. Survival analysis employed the Kaplan–Meier method, and the difference between strata was assessed for significance using log-rank tests. Patients treated with palliative intent were excluded from survival analysis when comparing approach to treatment with endoscopic or open surgery.

Results

Thirty-two cases of esthesioneuroblastoma were diagnosed between 1994 and 2013 (0.4 per million per year). Of these, 22 had been diagnosed between 2004 and 2013 compared with 10 between 1994 and 2003. A choropleth map of Ireland showing distribution of incidence is displayed in ►Fig. 1. Average age at diagnosis was 57 years; however, two cases were less than 20 years old. The majority of cases were male at 20/32 (62.5%). Median duration of follow-up was 67 months. Kaplan–Meier curve for overall survival is shown in ►Fig. 2. Overall, 5-year survival was 65%.

Patients were managed through a single-center multidisciplinary team. Presentation was predominantly with nasal congestion or epistaxis (73%), while two cases were identified incidentally on radiological investigations. Two patients with a tumor stage of Kadish D were treated with palliative intent. Primary treatment was non-surgical in three cases; one was treated with chemoradiation and two with radiation alone

Fig. 1 Choropleth map of number of esthesioneuroblastoma cases per county in Ireland.

Primary surgical management (two post neo-adjuvant treatment) was undertaken in 27 cases with 18 requiring bifrontal craniotomy. Postoperative radiation therapy was given to 24 patients. There was no endoscopic resection performed prior to 2008; however, since then six (50%) patients have been managed with endoscopic resection.

Metastasis to the neck, at level I, was seen in one patient 6 years post treatment for the primary tumor. This was managed by modified radical neck dissection, with the pathology confirming extracapsular extension. The patient received external beam irradiation of 60 Gy over 30 Fr unilaterally to the left neck and remains disease free at the latest follow-up. Metastases to the spine or the lungs were seen in three patients.

Kadish A/B patients exhibited 100% 5-year disease-specific survival compared with 54% in Kadish C/D ($p = 0.011$). Kaplan–Meier survival curves are shown in ►**Fig. 3**. Hyams grade I/II patients exhibited 75% 5-year disease-specific survival compared with 63% in Hyams grade III/IV ($p = 0.005$). Kaplan–Meier

survival curves are shown in ►**Fig. 4**. Patients treated endoscopically exhibited 100% 5-year disease-specific survival compared with 51% in those treated with open approach ($p = 0.102$). Kaplan–Meier survival curves are shown in ►**Fig. 5**.

There were 14 patients who suffered disease recurrence after primary curative treatment with time to recurrence ranging from 230 to 2257 days. Kadish A/B patients exhibited 70% 5-year recurrence-free survival compared with 41% in Kadish C/D ($p = 0.011$). Hyams grade I/II patients exhibited 64% 5-year recurrence-free survival compared with 31% in Hyams grade III/IV ($p = 0.005$). Interestingly, only one patient out of six treated endoscopically developed recurrence, at 386 days postoperatively. Patients treated endoscopically exhibited 83% 5-year recurrence-free survival compared with 40% in those treated with open approach ($p = 0.102$).

Fig. 2 Kaplan–Meier curve for overall survival.

Fig. 3 Kaplan–Meier disease-specific 5-year survival curves comparing Kadish stage A/B against Kadish stage C/D. These were evaluated by log-rank test ($\chi^2 = 6.538$, $p = 0.011$).

Fig. 4 Kaplan–Meier disease-specific 5-year survival curves comparing Hyams Grade I/II against Hyams Grade III/IV. These were evaluated by log-rank test ($\chi^2 = 7.814$, $p = 0.005$).

Fig. 5 Kaplan–Meier disease-specific 5-year survival curves comparing endoscopic against open surgical treatment. These were evaluated by log-rank test ($\chi^2 = 2.667$, $p = 0.102$).

Discussion

Irish results are mostly consistent with international literature pertaining to esthesioneuroblastoma, although a higher proportion of males appear to be affected in Ireland. As it is an uncommon malignancy, highly powered studies on the

diagnosis and treatment of esthesioneuroblastoma are difficult to produce. As a result, there are several areas of dispute in its management, which warrant further investigation with multicenter trials, such as the optimal management of the node negative neck at the initial presentation.

The complex phenotype, combined with the tumor rarity and variability in biologic activity from indolent to aggressive, leads to potential for misdiagnosis. Precise diagnosis is important to distinguish esthesioneuroblastoma from other similar sinonasal malignancies as prognosis is significantly different between them.²⁰ This relies on recognition of differential immunohistologic features of similar tumors as there is no immunocytochemical stain specific to esthesioneuroblastoma. Improved recognition of this tumor by contemporary histologic techniques may reflect increasing incidence.⁶ The increase of 220% between the two decades included in this study could be explained by improved pathological recognition in smaller centers with appropriate referral for specialist pathological input in diagnosis, although it is possible that referral pathways in general may have altered, contributing to higher detection rates. Diagnosis by a pathologist familiar with skull base malignancy is recommended because a thorough knowledge of the immunohistochemical staining pattern of similar tumors is important to differentiate esthesioneuroblastoma from other potential diagnoses.

Hyams introduced a grading system in 1998 to further characterize this tumor,²¹ based upon pathologic features, such as mitotic activity and necrosis, shown in ►Table 1. A meta-analysis of five studies demonstrated a significantly worse 5-year survival of 20% in Hyams grade III/IV versus 56% in Hyams grade I/II,²² and a more recent retrospective study of 281 patients revealed similar results.⁸ While the full breadth of the Hyams grading system in prognostication remains to be established, it is proving to be a valuable tool in characterizing tumor biology and, as it is an independent predictor of locoregionally aggressive disease and worse disease-free survival, it should be considered when contemplating adjuvant therapy.²³ Its value as a prognostic tool can be also seen in this study, with significantly improved survival in patients with a lower Hyams grade.

There is no overall consensus on staging systems for esthesioneuroblastoma with regard to correlating disease extent with prognosis and guiding treatment; however, several systems are described based on radiological findings. The first and mostly widely used staging system was proposed by Kadish in 1976.²⁴ As this failed to account for metastatic disease, it was modified by Morita in 1993 by addition of Stage

Table 1 Hyams grading system

Grade	Lobular architecture preservation	Mitotic index	Nuclear polymorphism	Fibrillary matrix	Rosettes	Necrosis
I	+	Zero	None	Prominent	Homer–Wright rosettes	None
II	+	Low	Low	Present	Homer–Wright rosettes	None
III	±	Moderate	Moderate	Low	Flexner–Wintersteiner rosettes	Rare
IV	±	High	High	Absent	None	Frequent

Table 2 Modified Kadish staging system

Stage	Extent
A	Tumor limited to the nasal cavity
B	Tumor in the nasal cavity and extending to the paranasal sinuses
C	Tumor extends beyond the nasal cavity and paranasal sinuses involving the cribriform lamina, the skull base, the orbit, or the intracranial cavity
D	Tumor with neck or distant metastases

D representing tumors with regional or distant metastasis at presentation and is shown in ►Table 2.²⁵ An alternative staging system was proposed by Dulguerov and Calcaterra in 1992,²⁶ based on a TNM format, as they considered Stage C in the modified Kadish system to be very broad in its definition. Biller also described a TNM-based staging system in 1990, which separated resectable and unresectable parenchymal brain disease.²⁷ These TNM-based systems have shown correlation with survival in some cases;^{28,29} however, most of the proposed staging systems are somewhat restrictive, and the utility of any of these currently described staging systems remains questionable.²³ Using the Kadish staging system in this study, a significantly worse survival was identified in patients with higher stage tumors.

Tumours most commonly present with unilateral nasal obstruction (70%) or epistaxis (50%), as demonstrated in this patient cohort, with less common symptoms including headaches, pain, excessive lacrimation, rhinorrhea, visual disturbances, and anosmia.⁹ There are several reported cases of paraneoplastic syndromes related to vasopressin- or catecholamine-secreting esthesioneuroblastomas.^{30,31} The majority of cases exhibit indolent growth; hence, symptoms may have been present for a prolonged period. Therefore, it is not surprising that incidental diagnosis on radiological investigation is often the initial presentation, as was the case with two patients in this study. Although there are extremely rare descriptions of ‘ectopic’ presentation of tumors in atypical locations of the nasal cavity, it should be assumed that all cases involve the cribriform plate unless histologically proven otherwise. Cervical lymph node or distant metastases appear to develop irrespective of tumor grade with lung and bone the most common sites for distant metastatic disease.⁹

As technology has advanced in sinonasal surgery, an increasing number of esthesioneuroblastoma cases are being successfully treated via endoscopic surgery. Pooled data have revealed improved outcomes in cases treated endoscopically, even when only considering advanced disease.³² Although survival outcomes are much better in endoscopically treated cases in this study, this is subject to selection bias as four out of six cases were Kadish B and two were Kadish C. The ultimate goal in surgery for these tumors is complete resection with clear margins, and this is crucial when selecting patients who are appropriate for resection with an endoscopic approach. Endoscopic surgery may be considered as an adjunct to an open approach or for palliative debulking in advanced cases.

Early diagnosis likely leads to improved survival; however, long-term prognosis appears to be good for the majority of cases due to their indolent nature, even despite disease recurrence or spread. This is reflected by the gap in results of recurrence-free and disease-specific survival rates in this study. A small number of studies recommend single modality therapy with either radiation or surgery in Kadish A tumors;^{33,34} however, the vast majority of studies suggest that combined modality therapy is most appropriate in the management of esthesioneuroblastoma as it has been reported to improve local tumor control, particularly in advanced stage and high-grade disease.^{35,36} Adjuvant radiation can be used alone or concurrently with chemotherapy postoperatively as cisplatin-based chemotherapy is active against esthesioneuroblastoma even in advanced stage and high-grade disease.^{22,37} Neoadjuvant treatment with chemotherapy and/or radiation may be of benefit in advanced disease;³⁸ however, further studies are necessary to determine its effectiveness.³⁹

Metastatic disease to the neck occurs in ~5% of cases of esthesioneuroblastoma and is a poor prognosticator.²² While rates of neck metastases on the initial presentation are low, the rate of regional failure post treatment of the primary site is as high as 20 to 25%.^{19,40} This is not seen in our study, with only one case of regional recurrence, managed successfully with neck dissection. This is also despite no cases undergoing elective neck dissection at the initial presentation. Combined modality treatment with selective neck dissection and post-operative radiation, with or without concurrent chemotherapy, is advocated to manage any node positive neck, whether at the initial presentation or as regional failure.¹⁹

Optimal management of patients who present with a node negative neck at the initial presentation is uncertain. Due to the high rate of regional failure, prophylactic treatment of the neck with selective neck dissection and/or radiation has been suggested in those considered high risk for metastatic spread such as Kadish stage B/C or Hyams grade III/IV.^{40–42} This is because it has been suggested that mortality from disease in patients with recurrence in cervical lymph nodes is significant when compared with those who never develop neck disease.⁴³ However, with a long time to presentation of regional failure and potential for good control from appropriate salvage treatment,^{3,44–46} a policy of observation and salvage therapy in the event of failure may be appropriate. Regarding neck irradiation, one study suggested that elective irradiation in those with a clinically negative neck could significantly reduce the risk of cervical nodal recurrence, but this did not translate to an overall survival benefit.⁴⁷ Unfortunately, there are no trials comparing prophylactic treatment of the neck versus observation and salvage therapy in the event of regional failure, but more studies reporting the prognosis of salvage therapy for regional failure may help guide future research.

As accurate diagnosis of this heterogeneous tumor improves, there may be scope for focused molecular studies to aid in diagnosis and treatment. A few molecular markers have been investigated, with Bcl-2 present in up to 65% of cases.⁴⁸ Bcl-2 has been studied in relation to grade and treatment with neoadjuvant therapy, showing a trend of expression in higher

Fig. 6 Optimal management of esthesioneuroblastoma. CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

grade tumors and predicting response to therapy.^{48,49} Retrovirus particles have been demonstrated in tumor rosettes of esthesioneuroblastoma in cats and transgenic mice, but it has yet to be established as to whether there is any link between viral infection and tumor pathogenesis in humans.²² No marker has yet proven clinically useful; therefore, multi-institutional and international collaboration, with centralization of cases, would offer a better chance at identifying molecular alterations to develop targeted therapy.²³ Meanwhile, the best practice is currently guided by mostly retrospective publications in the literature, with surgery and postoperative radiation considered as the gold standard of treatment.⁵⁰

Many controversies exist in the diagnosis and management of this condition, but a summary of optimal management, based on Irish and international results, is shown in **Fig. 6**. Results from Irish data are mostly concordant with international literature, demonstrating good outcomes for this disease if diagnosed early and treated appropriately. Due to the complexity and rarity of this disease, diagnosis and treatment should be in a tertiary referral center by appropriate multidisciplinary team members familiar with best practice in esthesioneuroblastoma management. Continued research and pooled data on this tumor will assist in the debate on the best approach for diagnosis and treatment.

Note

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Conflict of Interest

None.

References

- Berger L, Luc H, Richard R. L'esthesioneuro epitheliome olfactif. *Bull Assoc Fr Etud Cancer* 1924;13:410–420
- Theilgaard SA, Buchwald C, Ingeholm P, Kornum Larsen S, Eriksen JG, Sand Hansen H. Esthesioneuroblastoma: a Danish demographic study of 40 patients registered between 1978 and 2000. *Acta Otolaryngol* 2003;123(03):433–439
- Petrizzelli GJ, Howell JB, Pederson A, et al. Multidisciplinary treatment of olfactory neuroblastoma: patterns of failure and management of recurrence. *Am J Otolaryngol* 2015;36(04):547–553
- Shirzadi AS, Drazin DG, Strickland AS, Bannykh SI, Johnson JP. Vertebral column metastases from an esthesioneuroblastoma: chemotherapy, radiation, and resection for recurrence with 15-year followup. *Case Rep Surg* 2013;2013:107315
- 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(4A):2683–2706
- Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. *Arch Otolaryngol Head Neck Surg* 2007;133(03):276–280

- 7 Su SY, Bell D, Hanna EY. Esthesioneuroblastoma, neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma: differentiation in diagnosis and treatment. *Int Arch Otorhinolaryngol* 2014;18(Suppl 2):S149–S156
- 8 Tajudeen BA, Arshi A, Suh JD, St John M, Wang MB. Importance of tumor grade in esthesioneuroblastoma survival: a population-based analysis. *JAMA Otolaryngol Head Neck Surg* 2014;140(12):1124–1129
- 9 Thompson LD. Olfactory neuroblastoma. *Head Neck Pathol* 2009;3(03):252–259
- 10 Carney ME, O'Reilly RC, Sholevar B, et al. Expression of the human Achaete-scute 1 gene in olfactory neuroblastoma (esthesioneuroblastoma). *J Neurooncol* 1995;26(01):35–43
- 11 Ow TJ, Bell D, Kupferman ME, Demonte F, Hanna EY. Esthesioneuroblastoma. *Neurosurg Clin N Am* 2013;24(01):51–65
- 12 Hwang SK, Paek SH, Kim DG, Jeon YK, Chi JG, Jung HW. Olfactory neuroblastomas: survival rate and prognostic factor. *J Neurooncol* 2002;59(03):217–226
- 13 Song CM, Won TB, Lee CH, Kim DY, Rhee CS. Treatment modalities and outcomes of olfactory neuroblastoma. *Laryngoscope* 2012;122(11):2389–2395
- 14 Nabili V, Kelly DF, Fatemi N, St John M, Calcaterra TC, Abemayor E. Transnasal, transfacial, anterior skull base resection of olfactory neuroblastoma. *Am J Otolaryngol* 2011;32(04):279–285
- 15 Snyderman CH, Carrau RL, Kassam AB, et al. Endoscopic skull base surgery: principles of endonasal oncological surgery. *J Surg Oncol* 2008;97(08):658–664
- 16 Stammberger H, Anderhuber W, Walch C, Papaefthymiou G. Possibilities and limitations of endoscopic management of nasal and paranasal sinus malignancies. *Acta Otorhinolaryngol Belg* 1999;53(03):199–205
- 17 Folbe A, Herzallah I, Duvvuri U, et al. Endoscopic endonasal resection of esthesioneuroblastoma: a multicenter study. *Am J Rhinol Allergy* 2009;23(01):91–94
- 18 Tajudeen BA, Arshi A, Suh JD, et al. Esthesioneuroblastoma: an update on the UCLA experience, 2002–2013. *J Neurol Surg B Skull Base* 2015;76(01):43–49
- 19 Zanation AM, Ferlito A, Rinaldo A, et al. When, how and why to treat the neck in patients with esthesioneuroblastoma: a review. *Eur Arch Otorhinolaryngol* 2010;267(11):1667–1671
- 20 Rosenthal DI, Barker JL Jr, El-Naggar AK, et al. Sinonasal malignancies with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Cancer* 2004;101(11):2567–2573
- 21 Hyams V, Batsakis J, Michaels L. Olfactory neuroblastoma. Tumors of the Upper Respiratory Tract and Ear, Atlas of Tumor Pathology. vol 25. Washington DC: Armed Forces Institute Press; 1988:240–248
- 22 Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol* 2001;2(11):683–690
- 23 Saade RE, Hanna EY, Bell D. Prognosis and biology in esthesioneuroblastoma: the emerging role of Hyams grading system. *Curr Oncol Rep* 2015;17(01):423
- 24 Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer* 1976;37(03):1571–1576
- 25 Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. *Neurosurgery* 1993;32(05):706–714, discussion 714–715
- 26 Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970–1990. *Laryngoscope* 1992;102(08):843–849
- 27 Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: surgical treatment without radiation. *Laryngoscope* 1990;100(11):1199–1201
- 28 Zafereo ME, Fakhri S, Prayson R, et al. Esthesioneuroblastoma: 25-year experience at a single institution. *Head Neck Surg* 2008;138(04):452–458
- 29 Bachar G, Goldstein DP, Shah M, et al. Esthesioneuroblastoma: The Princess Margaret Hospital experience. *Head Neck* 2008;30(12):1607–1614
- 30 Senchak A, Freeman J, Ruhl D, Senchak J, Klem C. Low-grade esthesioneuroblastoma presenting as SIADH: a review of atypical manifestations. *Case Rep Otolaryngol* 2012;2012:582180
- 31 Salmasi V, Schiavi A, Binder ZA, et al. Intraoperative hypertensive crisis due to a catecholamine-secreting esthesioneuroblastoma. *Head Neck* 2015;37(06):E74–E80
- 32 Fu TS, Monteiro E, Muhanna N, Goldstein DP, de Almeida JR. Comparison of outcomes for open versus endoscopic approaches for olfactory neuroblastoma: a systematic review and individual participant data meta-analysis. *Head Neck* 2016;38(Suppl 1):E2306–E2316
- 33 Shah JP, Patel SG, Singh B. Skull base. In: Shah JP, ed. *Jatin Shah's Head and Neck Surgery and Oncology*. Philadelphia, PA: Elsevier; 2007:171
- 34 Benfari G, Fusconi M, Ciofalo A, et al. Radiotherapy alone for local tumour control in esthesioneuroblastoma. *Acta Otorhinolaryngol Ital* 2008;28(06):292–297
- 35 Foote RL, Morita A, Ebersold MJ, et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 1993;27(04):835–842
- 36 De Bonneau G, Lepage B, Rimmer J, et al. Long-term carcinologic results of advanced esthesioneuroblastoma: a systematic review. *Eur Arch Otorhinolaryngol* 2016;273(01):21–26
- 37 Bradley PJ, Jones NS, Robertson I. Diagnosis and management of esthesioneuroblastoma. *Curr Opin Otolaryngol Head Neck Surg* 2003;11(02):112–118
- 38 Polin RS, Sheehan JP, Chenelle AG, et al. The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: the University of Virginia experience. *Neurosurgery* 1998;42(05):1029–1037
- 39 Sohrabi S, Drabick JJ, Crist H, Goldenberg D, Sheehan JM, Mackley HB. Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: a case series and review of the literature. *J Clin Oncol* 2011;29(13):e358–e361
- 40 Ferlito A, Rinaldo A, Rhys-Evans PH. Contemporary clinical commentary: esthesioneuroblastoma: an update on management of the neck. *Laryngoscope* 2003;113(11):1935–1938
- 41 Demiroz C, Gutfeld O, Aboziada M, Brown D, Marentette LJ, Eisbruch A. Esthesioneuroblastoma: is there a need for elective neck treatment? *Int J Radiat Oncol Biol Phys* 2011;81(04):e255–e261
- 42 Banuchi VE, Dooley L, Lee NY, et al. Patterns of regional and distant metastasis in esthesioneuroblastoma. *Laryngoscope* 2016;126(07):1556–1561
- 43 Naples JG, Spiro J, Tessema B, Kuwada C, Kuo CL, Brown SM. Neck recurrence and mortality in esthesioneuroblastoma: implications for management of the NO neck. *Laryngoscope* 2016;126(06):1373–1379
- 44 Gore MR, Zanation AM. Salvage treatment of late neck metastasis in esthesioneuroblastoma: a meta-analysis. *Arch Otolaryngol Head Neck Surg* 2009;135(10):1030–1034
- 45 Ohtakara K, Hoshi H. Long-term tumor control despite late pseudoprogression on (18)F-FDG-PET following extremely hypofractionated stereotactic radiotherapy for retropharyngeal lymph node metastasis from esthesioneuroblastoma. *Case Rep Oncol* 2014;7(02):576–582
- 46 Simon JH, Zhen W, McCulloch TM, et al. Esthesioneuroblastoma: the University of Iowa experience 1978–1998. *Laryngoscope* 2001;111(03):488–493
- 47 Jiang W, Mohamed AS, Fuller CD, et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. *Pract Radiat Oncol* 2016;6(04):241–247
- 48 Diensthuber M, Potinius M, Rodt T, et al. Expression of bcl-2 is associated with microvessel density in olfactory neuroblastoma. *J Neurooncol* 2008;89(02):131–139
- 49 Fukushima S, Sugita Y, Niino D, Mihashi H, Ohshima K. Clinicopathological analysis of olfactory neuroblastoma. *Brain Tumor Pathol* 2012;29(04):207–215
- 50 Bak M, Wein RO. Esthesioneuroblastoma: a contemporary review of diagnosis and management. *Hematol Oncol Clin North Am* 2012;26(06):1185–1207