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Case Report

Management of Esthesioneuroblastoma: Past, present and future

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Introduction

Esthesioneuroblastoma, also known as olfactory neuroblatoma, is a primitive neuroectodermal tumor of the upper nasal cavity that it is thought to arise from the olfactory epithelium. Classically, it exhibits locally aggressive behavior accounting for 3% of intranasal neoplasms, however it can present with a wide variety of clinical behavior. [10,11,22,28]. The most frequent sites of initial presentation are the upper aspect of the nasal cavity (ethmoidal area), followed by the maxillary sinus, nasopharynx, and the pituitary area [10,11,28]

Clinically, the most common symptoms are unilateral or bilateral nasal obstruction and anterior nasal discharge often reported as a serosanguinous discharge with pieces of necrotic tissue. Pain is rare and is caused by local invasion of adjacent structures, mainly bone or nerves. Proptosis, epiphora and diplopia are later signs of orbital involvement. Olfactory disorders are also common, in the form of cacosmia or dysosmia [4,10,11,28]. There is a bimodal age distribution, with peaks during the second and sixth decades of life, although it has been reported in all ages [10].

Histologically, most of them are considered high grade. The tumor typically is composed of round, oval, or fusiform cells containing neurofibrillary elements with pseudorosette formation and diffusely increased microvascularity.

Histopatholical grade, as determined by Hyams, is the most important prognostic factor [34]. The median survival was 56% in patients with grades 1 or 2 and 25% in those with grades 3 or 4. This difference was found to be significant in a retrospective study [11]. Other important prognostic factors are tumor size, intra cranial extension, nodal involvement and the histological grade [10,11,28].

Local recurrence after primary surgery is the more frequent event at rates of about 30%. Regional recurrence with local tumor control occurs in 15% to 20% of cases [11,28]. Metastases occur in 14% to 35% of patients, most commonly in cervical lymph node chains, lung and bone. [10,17,28]. There is a correlation between local tumor extension, metastatic disease and survival in these patients. [11,17,28]

Magnetic resonance imaging and computed tomography are of paramount importance to assess tumor extension and to plan loco-regional treatment [11,28]. The staging system used is the modified Kadish system. (Table 1) [19]

	Kadish MODIFIED SYSTEM
A	Disease confined to the nasal cavity
B	Disease confined to the nasal cavity and one or more par nasal sinuses
C	Disease extended out of the nasal cavity and / or sinuses, including orbit, skull base or intracranial cavity.
D	A positive cervical nodes or distant metastases

Table 1. Kadish system of Esthesioneuroblastoma staging

An extensive review of the literature was performed by Kane in 2010 [20] identifying 205 published studies reporting on 956 patients. The data were reanalyzed due to the absence of class I or II data due to the overal rarity of ENB, in an attempt to ascertain what variables can predict prognosis in these patients and to determine the relative effect of different therapies. [20]

The “standard approach” as initial management of ENB is a combination of surgery followed by radiotherapy in selected cases [3,4,10,11,13,22,28,31,34]. Surgical resection entails, in most cases, a craniofacial. It is important to note that the best results published in disease-free survival have been achieved with this combination of surgery and adjuvant radiotherapy [8,9,19,25].

Introduction of craniofacial resection in the management of ENB in the 1960s was associated with significant improvement in prognosis [1,11,22,28] and it still represents the gold standard [5]. Nevertheless, complete tumor removal cannot be achieved in approximately one third of the patients [9,12,27] which necessitates adjuvant postoperative treatment. Unfortunately the procedure has been associated with non negligible postoperative complications (36.3%) and perioperative morality rates (7%) [16]. Resection of the tumor often entails removal of the cribriform plate, dura adjacent and olfactory bulbs. In the case of orbital involvement wide resection is performed and in extreme cases even orbital exenteration [25].

Author	Patients (n)	Kadish Stage	Treatment	5-year overall survival (%)
Resto et al. 2000 (22)	27		S, PORT	
Chao et al. 2001 (4)	25		S,RT,CHT	66
Oskouian et al. 2002 (18)	34	A/B	S, pre-op RT	81
		C	S, pre-op RT, post-op CHT	
Theilgaard et al. 2003 (24)	40	A/B	S,RT	61
		C	S,RT,CHT	
Constantinidis et al. 2004 (5)	25	A	S	72
		B/C	S,RT, +/-CHT	
Diaz et al. 2005 (6)	30		S, PORT	89
Rastogi et al. 2006 (21)	8	C/B	RT, CHT	62.5*
McLean et al. 2007 (15)	21	B	S, PORT, post-op CHT	71.4
		C	S, PORT, post-op CHT	75
Benfari et al. 2008 (1)	55	A	RT	100
		B	RT	58.3
		C	RT	18.9
Kane et al. 2010 (12)	574	A	S, +/-RT	86
		B	S, +/-RT	80
		C	S, +/-RT	64
Monteiro et al. 2011 (16)	4	B/C/D	S, PORT	
Ow et al. 2013 (19)	70	C/D	S	10.5
		C/D	PORT	11.6

Table 2. **Results of literature review for various treatment modalities for primary treatment.** S = surgery, RT = radiotherapy, PORT = post-operative radiotherapy, pre-op = pre-operative, CHT = chemotherapy, * indicates 3 year survival rate

Recent advances in endoscopic skull base surgery have shown effectivenes in cancers involving the anterior skull base with limited intracranial extension [17,33], but the majority of cases with dural invasion, transdural growth and brain invasion do stil require a craniofacial approach [10,14,17]. Endoscopic endonasal surgery, in properly selected patients, can be considered as a sound alternative to traditional open approaches, with comparable oncological control rates, shorter hospital stays, reduced morbidity and fewer complications. [5,12,].

Quality of life decreases sharply after the first postoperative month and tends to improve over the course of 1 year until it reaches at least partial recovery [5]

Radiotherapy is indicated in low-grade tumors with positive or close margins, residual or recurrent disease and for all high-grade tumors despite the degree of resection or nodal involvement. [3,10,11,13,22]. In addition, for high-grade tumors chemotherapy should be considered, due to its poor prognosis [10,11].

No studies support the use of chemotherapy as a single modality in potentially curative cases, due in part to the small number of reported patients treated [3,11]. However, it is used as part of schemes of chemoradiation, as a sensitizer or in the palliative setting. The most commonly used drugs are thiotepa, cyclophosphamide, vincristine, dacarbazine, fluorouracil, methotrexate, cisplatin, etoposide, lomustine and doxorubicin or their combinations [3,11].

For advanced or unresectable cases, exclusive chemoradiation might be the best choice.

As mentioned previously, radiation therapy is often the cornerstone of the treatment. It is important to have a detailed image of the anatomy and a complete understanding of patterns of tumor growth. MRI (usually T1 images with Gd) with coronal, sagital and axial reconstructions are of paramount importance to determine tumor extension as well as anatomic relationships (medial wall of the orbit, extension into the nasal cavity, extension into the anterior cranial fossa, involvement of the ethmoidal, maxillary sinus and pterigomaxillary and pterigopalatine fossae).

Regarding treatment modality, Intensitiy Modulated Radiation Therapy is the most modern technique that can effecively treat tumors in this location. Dynamic modulation of the beam with the volumetric arc therapy technique offers the highest degree of conformality. The use of Image guidance techniques such as cone beam CT do offer the advantage of highly accure set up that allows the radiation oncologist to minimize the margin arround the tumor volume.

The complexity of the treatment starts with the patient positioning. Due to the complex anatomical location, the identification of the optic pathway as an organ at risk. It is important to instruct the patient to maintain a straight forward gaze at the time of the virtual simulation and treatment. In older techniques, in an attempt to preserve the lens, the patient was instructed to look sideways. This is not recommended since it may expose the optic nerve medially due to the rotation of the ocular globe, introducing the optic nerve in the high dose area. Extreme care should be taken to identify the lacrimal gland and the optic apparatus from the papilla all the way to the chiasm [31]. The recommended doses are between 55-65 Gy [8,17,23].

In recent times it has been shown that stereotactic techniques may play as a boost or

to manage early recurrence. [25,34] Stereotactic Radiosurgery is increasingly being used to treat a variety of head and neck tumors because of its highly conformal dose distributions and stereotactic spatial accuracy in delivery. SBRT is technically feasible, well tolerated and compares favorably to other alternatives of salvage therapy in the management of patients with recurrent and/or previously irradiated head and neck cancers, including anterior cranial fossa tumors [21,33].

Case Report

1. December 2009: a 29 y/o Caucasian Female presented at the Otolaryngology service with sinusitis, hypertelorism and exophthalmos showing a few months of development. A T1 Gd-enhanced MRI showed a solid lesion of 70 mm x 64 mm originating in the cribiform plate that had invaded the anterior cranial fossa, upper ethmoidal cells, nasal cavity, nasopharynx and the maxillary sinuses. Posteriorly, the lesion extended through the coanae and sphenoid sinus. There was an invasion of both orbits laterally due to extension through the lamina papiracea of the ethmoidal bone, with displacement of the medial rectus and invading preseptal fat. (Figure 1)
2. February 2010: biopsy informs undifferentiated malignancy, compatible with esthesioneuroblastoma. This was confirmed by IHC and the patient was staged as EC.
3. March 2010: MRI Control (23/04/10) revealed facial mass with postsurgical changes in the nasal cavity and nasal fossa. Multilobulated solid formations that enhanced after contrast administration, displacing the medial and rectus muscle were observed. There was another mass in the nasopharynx with lateral extension, invading the ipsilateral pterygoid space. (Figure 2).
4. May 2010: radiation treatment is performed concomitantly with a weekly dose of cisplatin 50 mg. Radiation therapy 3DCRT technique was used with an initial PTV covering the base of the skull and sinuses at the dose of 50 Gy with daily doses per fraction of 2 Gy. This was followed by a 16 Gy boost to the areas of known disease, with the same fractionation. Energy used was 6 MV photons. Her treatment was completed in July 2010 (Figure 3).
5. January 2011: an asymptomatic patient with control MRI reports that indicate the presence of two space-occupying lesions that enhance contrast. The first lesion was in the left temporal lobe of size 46 mm x 21 mm x 42 mm. The second lesion was 8 mm in diameter at the level of the internal table in the right frontoparietal junction. This was compatible with brain metastases.
6. February 2011: complete surgical resection of both lesions was performed. Pathology: neuro epithelial tumor metastasis primitive.
7. May 2011: adjuvant 3DCRT treatment was provided to both surgical beds for a total dose of 40 Gy.
8. February 2012: Asymptomatic patient control MRI reports show nodular enhancement of the duramadre at the level of the right parietal convexity with maximum diameter of 40 mm. This was compatible with metastases.
9. March 2012: during a planning MRI, found another left parietal lesion 2 cm in diameter. Treatment was performed in both lesions. Total dose 15 Gy (60% isodose). (Figure 4)
10. August 2012: a brain MRI reveals two solid expansive lesions probably extra-axial of dural implantation. The first one frontal and left parietal and another more extensive, in the fronto-temporal region right-parietal. New brain relapse. Patient decides palliative measures.
11. February 2013: death by neurogical causes.

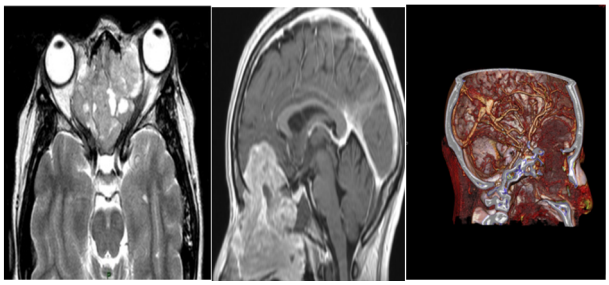

Figure 1 T1 Gd-enhanced MRI showing a solid lesion originating in the cribiform plate that invaded the anterior cranial fossa, upper ethmoidal cells, nasal cavity, nasopharynx and the maxillary sinuses.

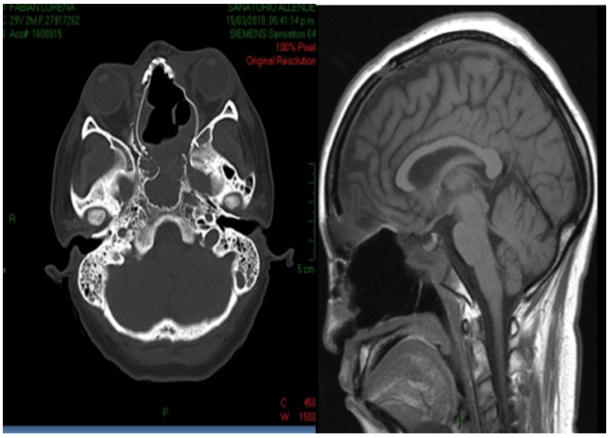

Figure 2. T1 Gd-enhanced MRI revealing a mass in the nasopharynx with lateral extension, invading the ipsilateral pterygoid space.

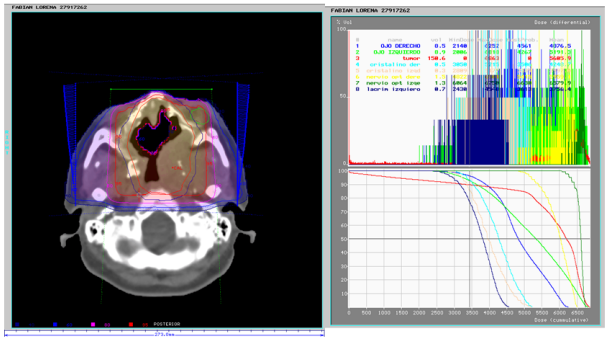

Figure 3. T1 Gd-enhanced MRI image after 3DCRT radiation treatment was performed concomitantly with a weekly dose of cisplatin 50mg.

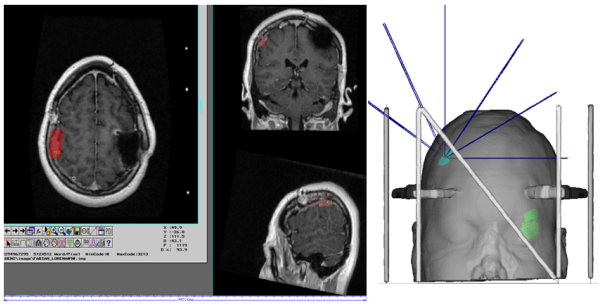

Figure 4. T1 Gd-enhanced MRI revealing a left parietal lesion 2 cm in diameter.

Discussion

In a recent series of 42 patients (Lund et al), craniofacial resection with adjuvant radiotherapy showed actuarial disease-free survival of 71% at 5 years and 53% at 10 years when the tumor was confined to the nasal cavity and skull base.

Eden et al [12] found no significant difference in survival when comparing pre-and postoperative radiotherapy. However, they showed better local control with preoperative radiotherapy. This was confirmed by Spaulding et al [28] and it was attributed to the introduction of more sophisticated techniques such as craniofacial resection and the image-guided radiotherapy.

Since the incidence of cervical lymph node metastasis in early stages is less than 10%, elective irradiation or neck dissection is not recommended. However, in patients with stage C, where metastases in the lymph nodes is more than 44%, the suggested treatment is radiation and/or radical neck dissection. Relapse rates were between 5.8% and 62%, and they are present in the first two years (86%) [4,10,11,31].

The debate about the optimal therapy for ENB has not been resolved yet. There are strong advocates of radiotherapy alone, surgery alone, and combined modality including chemotherapy.

In stage C, and in high-grade tumors (Hyman 3-4), we believe there is a benefit in local control, obtained by the addition of adjuvant radiotherapy. As reported earlier, the most important factors of overall survival, disease-free survival and local recurrence are Grade, age, sex, and stage of Kadish.

According to Foote [15], local control improved in patients who obtained complete surgical resection plus postoperative adjuvant radiation when compared with patients receiving only surgery. Chemotherapy has been used mainly as an adjuvant in high grade tumors, positive margins, or in inoperable lesions [3,34].

Conclusions

1. The evolution of anterior skull base surgery calls for a holistic evaluation of outcomes, not limited to survival rates alone, but QOL and functional outcomes.
2. The most effective treatment is surgical resection with adjuvant or neoadjuvant radiotherapy. Whenever possible endoscopic skull base techniques should be used.
3. For malignant tumors, benign incompletely resected, recurrent tumors, and those with nodal extension, adjuvant radioterapy should be considered. The treatment volume must be individualized for each patient and must include the original extent of the primary tumor with an adequate margin.
4. Robust imaging is needed for planning and the use of IMRT with IGRT is recommended.
5. Chemotherapy is used mainly as an adjunct in high grade lesions (Hyams grade 3-4) or positive margins..
6. The staging by Kadish and hyman grade, have proven to be the most important prognostic factors.
7. The recommended dose of radiation is 60-65 Gy in the postop setting.

References

1. Benfari G, Fusconi M, Ciofalo A, Gallo A, Altissimi G, *et al.* (2008). Radiotherapy alone for local tumour control in esthesioneuroblastoma. *Acta Otorhinolaryngol Ital*, 28(6): 292-297.
2. Biller HF, Lawson W, Sachdev VP, Som P (1990). Esthesioneuroblastoma: surgical treatment without radiation. *Laryngoscope*, 100(11): 1199-1201.
3. Bhattacharyya N, Thornton AF, Joseph MP, Goodman ML, Amrein PC (1997). Successful treatment of esthesioneuroblastoma and neuroendocrine carcinoma with combined chemotherapy and proton radiation. Results in 9 cases. *Arch Otolaryngol Head Neck Surg*, 123(1): 34-40.
4. Broich G, Pagliari A, Ottaviani F (1997). Esthesioneuroblastoma: a general review of the cases published since the discovery of the tumour in 1924. *Anticancer Res*, 17(4A): 2683-2706.
5. Castelnuovo P, Lepera D, Turri-Zanoni M, Battaglia P, Bolzoni Villaret A, *et al.* (2013). Quality of life following endoscopic endonasal resection of anterior skull base cancers. *J Neurosurg*, 119(6): 1401-1409.
6. Chao KS, Kaplan C, Simpson JR, Haughey B, Spector GJ, *et al.* (2001). Esthesioneuroblastoma: the impact of treatment modality. *Head Neck*, 23(9): 749-757.
7. Chernov M, Muragaki Y, Kubo O, Hori T (2004). Advanced olfactory neuroblastoma wit intracranial extensión: report of two cases and search for an optimal managment *Neuro-Oncology (Tokyo)*, 14:57-63.
8. Constantinidis J, Steinhart H, Koch M, Buchfelder M, Schaenzer A, *et al.* (2004). Olfactory neuroblastoma: the University of Erlangen-Nuremberg experience 1975-2000. *Otolaryngol Head Neck Surg*, 130(5): 567-574.
9. de Almeida JR, Vescan AD, Gullane PJ, Gentili F, Lee JM, Lohfeld L, (2012). Development of a disease specific quality of life questionnaire for anterior and central skull base pathology- the skull base inventory *Laryngoscope*, 122:1933-1942.
10. Diaz EM Jr, Johnigan RH 3rd, Pero C, El-Naggar AK, Roberts DB, *et al.* (2005). Olfactory neuroblastoma: the 22-year experience at one comprehensive cancer center. *Head Neck*, 27(2): 138-149.
11. Dulguerov P, Calcaterra T (2001). Esthesioneuroblastoma: a meta análisis and review *Lancet*, 2: 683 -90.
12. Eden B, Debo R (1994). Esthesioneuroblastoma long term outcome and patterns of failure the University of Virginia. *Experience. Cancer.*, 73: 2556 – 2562.
13. Eich HT, Staar S, Micke O, Eich PD, St?tzer H, *et al.* (2001). Radiotherapy of esthesioneuroblastoma. *Int J Radiat Oncol Biol Phys*, 49(1): 155-160.
14. Feiz-Erfan I, Suki D, Hanna E, DeMonte F (2007). Prognostic significance of transdural invasion of cranial base malignancies in patients undergoing craniofacial resection. *Neurosurgery*, 61(6): 1178-1185.
15. Foote RL, Morita A, Ebersold MJ, Olsen KD, Lewis JE, *et al.* (1993). Esthesioneuroblastoma: the role of adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys*, 27(4): 835-842.
16. Ganly I, Patel SG, Singh B, Kraus DH, Bridger PG, *et al.* (2005). Complications of craniofacial resection for malignant tumors of the skull base: report of an International Collaborative Study. *Head Neck*, 27(6): 445-451.
17. Hanna E, DeMonte F, Ibrahim S, Roberts D, Levine N, *et al.* (2009). Endoscopic resection of sinonasal cancers with and without

craniotomy: oncologic results. *Arch Otolaryngol Head Neck Surg*, 135(12): 1219-1224.
18. Hyams VJ, Batsakis JG, Michaels L (eds) (1988). Tumors of the upper respiratory tract and ear *Atlas of Tumor Pathology, Second Series, Fascicle 25. Washington, DC: Armed Forces Institute of Pathology*, pp 240-248.
19. Kadish S, Goodman M, Wang CC (1976). Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer*, 37(3): 1571-1576.
20. Kane AJ, Sughrue ME, Rutkowski MJ, Aranda D, Mills SA, *et al.* (2010). Posttreatment prognosis of patients with esthesioneuroblastoma. *J Neurosurg*, 113(2): 340-351.
21. Lim CM, Clump DA, Heron DE, Ferris RL (2013). Stereotactic Body Radiotherapy (SBRT) for primary and recurrent head and neck tumors. *Oral Oncol*, 49(5): 401-406.
22. Lund VJ, Howard D, Wei W, Spittle M (2003). Olfactory neuroblastoma: past, present, and future? *Laryngoscope*, 113(3): 502-507.
23. McLean JN, Nunley SR, Klass C, Moore C, M?ller S, *et al.* (2007). Combined modality therapy of esthesioneuroblastoma. *Otolaryngol Head Neck Surg*, 136(6): 998-1002.
24. Monteiro EM, Lopes MG, Santos ER, Diniz CV, Albuquerque AS, *et al.* (2011). Endoscopic treatment of esthesioneuroblastoma. *Braz J Otorhinolaryngol*, 77(2): 171-177.
25. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, *et al.* (1993). Esthesioneuroblastoma: prognosis and management. *Neurosurgery*, 32(5): 706-714.
26. Oskouian RJ, Jane JA, Dumont AS (2002). Esthesioneuroblastoma: clinical presentation, radiological and pathological features, treatment, review of the literature, and the University of Virginia experience *Neurosurg Focus*, 12:1–9.
27. Ow TJ, Bell D, Kupferman ME, Demonte F, Hanna EY (2013). Esthesioneuroblastoma. *Neurosurg Clin N Am*, 24(1): 51-65.
28. Perez CA, Clifford Chao KS. (1998). Unusual nonepithelial tumors of the head and neck *Perez CA, Brady LW editors. Principles and Practice of Radiation Oncology, 3rd edition. Philadelphia: Lippincott-Raven Publishers*, p. 1111–1116.
29. Rastogi M, Bhatt M, Chufal K, Srivastava M, Pant M, Srivastava K, Mehrotra S (2006). Esthesioneuroblastoma Treated with Non-Craniofacial Resection Surgery Followed by Combined Chemotherapy and Radiotherapy: An Alternative Approach in Limited Resources *Jpn J Clin Oncol*, 36(10)613–619.
30. Resto VA, Eisele DW, Forastiere A, Zahurak M, Lee DJ, *et al.* (2000). Esthesioneuroblastoma: the Johns Hopkins experience. *Head Neck*, 22(6): 550-558.
31. Spaulding CA, Kranyak MS, Constable WC, Stewart FM (1988). Esthesioneuroblastoma: a comparison of two treatment eras. *Int J Radiat Oncol Biol Phys*, 15(3): 581-590.
32. Theilgaard SA, Buchwald C, Ingeholm P, Kornum Larsen S, Eriksen JG, *et al.* (2003). Esthesioneuroblastoma: a Danish demographic study of 40 patients registered between 1978 and 2000. *Acta Otolaryngol*, 123(3): 433-439.
33. Unger F, Haselsberger K, Walch C, Stammberger H, Papaefthymiou G (2005). Combined endoscopic surgery and radiosurgery as treatment modality for olfactory neuroblastoma (esthesioneuroblastoma). *Acta Neurochir (Wien)*, 147(6): 595-601.
34. Van Gompel JJ, Carlson ML, Pollock BE, Moore EJ, Foote RL, *et al.* (2013). Stereotactic radiosurgical salvage treatment for locally recurrent esthesioneuroblastoma. *Neurosurgery*, 72(3): 332-339.
35. Villano JL, Bressler L, Propp JM, Valyi-Nagy T, Martin IK, *et al.* (2010). Descriptive epidemiology of selected olfactory tumors. *J Neurooncol*, 100(1): 73-80.
36. Ward PD, Heth JA, Thompson BG, Marentette LJ (2009). Esthesioneuroblastoma: Results and Outcomes of a Single Institution's Experience. *Skull Base*, 19(2): 133-140.