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REVIEW ARTICLE

Olfactory neuroblastoma (esthesioneuroblastoma): towards minimally invasive surgery and multi-modality treatment strategies – an updated critical review of the current literature

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Summary

Olfactory neuroblastoma (esthesioneuroblastoma) was first described by Berger and Luc in 1924. It is considered to be an uncommon malignancy of the nasal cavity. The tumor arises from the specialized sensory epithelial olfactory cells, normally situated at the upper part of the nasal cavity, including the superior nasal concha, the roof of the nose and the cribriform plate.

The imaging modalities of choice are computed tomography (CT) and magnetic resonance imaging (MRI). Combination of surgery and radiotherapy (either conventional radiotherapy or stereotactic radiosurgery), with or without chemotherapy is considered to be the standard of care for primary site disease by the majority of researchers. Combined transfacial and neurosurgical conventional approaches are also adopted in many reported cases, mainly due to the endocranial extension and the close anatomic relationship of esthesioneuroblastomas with the ethmoid roof and cribriform plate. Recent literature supports that endoscopic resection correlates with similar oncologic control rates compared with conventional open surgery, provided that basic oncologic surgical principles with clearance of margins and intradural dissection (when required) are completely maintained.

Key words: *esthesioneuroblastoma, nasal cavity tumors, olfactory epithelium, olfactory neuroblastoma*

Introduction

Olfactory neuroblastoma, also referred as esthesioneuroblastoma, was first described by Berger and Luc in 1924 [1]. It is considered to be an uncommon malignancy of the nasal cavity. The tumor arises from the specialized sensory epithelial olfactory cells, normally situated at the upper part of the nasal cavity, including the superior nasal concha, the roof of the nose and the cribriform plate [2-4]. The disease generally occurs between the 5th and 6th decade of life. However, some authors support that, in the vast majority of the reported cases, a bimodal distribution (in the 2nd and 6th decade) is quite likely to be present. Sporadic cases have also been reported in children less than 10 years of age. Olfactory neuroblastoma comprises about 2-6% of the cases of paranasal sinus and nasal cavity tumors, and 0.3% of upper digestive tract malignancies [2-4]. The incidence of the tumor is reported to be approximately 0.4 per million of population [3,4]. Treatment recommendations range from minimally invasive endoscopic approaches to combined modality aggressive treatment, including craniofacial resection plus chemo-radiotherapy [5]. However, the progress of functional endoscopic sinus surgery during the last decades, in terms of both surgical techniques and technological advances (such as navigation systems), has made endoscopic resection very popular, as well as feasible and effective, in selected cases [5-7]. Such surgical approaches are usually combined with stereotactic radiosur-

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gery or adjuvant postoperative radiotherapy [8].

The aim of this article was to review the current literature with regard to diagnosis and treatment strategies suggested for managing such uncommon malignancies, mainly focusing on the specific role and indications of endoscopic resection and postoperative radiotherapy/radiosurgery.

Methods

An extensive search of the literature was performed for articles included in the following databases and electronic libraries:

Pubmed, Medline, Google Scholar and Cochrane databases. Key words used in this search were esthesioneuroblastoma, olfactory neuroblastoma, nasal cavity tumors and olfactory epithelium.

The results retrieved were categorized in 4 main categories:

a) presentation of the commonly used diagnostic and imaging modalities,

b) description and evaluation of the most frequently used staging systems,

c) comparative evaluation of the surgical approaches involved in the treatment of olfactory neuroblastomas and

d) assessment of the efficacy of multi-modality treatment strategies on both local disease control and overall survival rates.

Results-Discussion

Although the neural or neural crest origin of olfactory neuroblastoma is generally supported, it is quite interesting that little evidence has linked such tumors directly to the olfactory epithelium. The exact cell of origin of esthesioneuroblastomas is thought to be the basal reserve cell, which gives rise to the neuronal and epithelial sustencular cells [3-5].

Histopathology

Histopathologically, one of the most important and characteristic features is a lobular architecture comprised of primitive neuroblastoma cells [4,5,9]. Such circumscribed lobules or nests are identified below an intact mucosa separated by a vascularized fibrous stroma. The nuclei are usually small and uniform with hyperchromatic, albeit delicate, "salt and pepper" nuclear chromatin distribution. Nucleoli are inconspicuous. Cellular nests are surrounded by fine fibrovascular septa in an organoid fashion. Tumors are separated into 4 grades. However, strict definition of grade is often arbitrary. The grading is basically based on the degree of differentiation, presence of neural stroma, mitotic figures and necrosis. As far as the immunohistochemical features of olfactory neuroblastomas are concerned, such tumors are usually positive for synaptophysin, chromogranin, CD56, neuron specific enolase and S-100 protein. A few tumors may also stain for low molecular weight cytokeratin. However, they are negative for desmin, myogenin, CD45RB and CD99. Proliferation marker studies using Ki-67 show a high proliferative index of 10-50% [9].

Symptoms & clinical signs

As far as the symptomatology of such lesions is concerned, unilateral nasal obstruction and epistaxis are most commonly encountered, reported in approximately 70% and 50% of presented cases, respectively (Table 1) [3-5]. Smell impairment is not a common symptom, probably due to the presence of normal olfactory epithelium on the contralateral side. Headaches, excessive lacrimation or pain could be reported by some patients, although they are considered to be less common signs and symptoms [5].

Differential diagnosis

Differential diagnosis (Table 2) include squamous cell carcinoma, sinonasal undifferentiated carcinoma, extranodal natural killer/T-cell lymphoma, rhabdomyosarcoma, Ewing's sarcoma, mucosal malignant melanoma and neuroendocrine carcinomas. Other tumors that should also be considered in the differential diagnosis are paragangliomas, extramedullary plasmacytomas pituitary adenomas, extracranial meningiomas, mesenchymal chondrosarcomas and granulocytic sarcomas [2-5,10].

Table 1. Reported symptoms and clinical signs of esthesioneuroblastoma

Symptoms & clinical signs	*%*
Unilateral nasal obstruction	70
Unilateral epistaxis	50
Smell impairment	10-15
Headache	8-12
Excessive lacrimation	5-10
Facial pain	10-15

Table 2. Differential diagnosis for esthesioneuroblastoma

Differential diagnosis
Squamous cell carcinoma
Sinonasal undifferentiated carcinoma
Extranodal natural killer/T cell lymphoma
Rhabdomyosarcoma
Ewing's sarcoma
Mucosal malignant melanoma
Neuroendocrine carcinoma
Paraganglioma
Extramedullary plasmacytoma
Pituitary adenoma
Extracranial meningioma
Mesenchymal chondrosarcoma
Granulocytic sarcoma

Imaging studies

Most authors agree that the imaging modality of choice is the combination of CT and MRI (Table 3) [5,11-13]. The protocols for CT include axial and coronal scans of 1-5 mm thick slices with intravenous contrast agent. CT usually shows a characteristic "dumbbell-shaped" mass extending across the cribriform plate [13]. Erosion of the lamina papyracea or cribriform plate is revealed by non contrast methods. Contrast CT scan usually shows homogeneous masses with necrotic non enhancing areas [12,13]. MRI, with or without contrast, is very helpful in identifying the extent of the tumor to adjacent sites, especially when tumor spread into surrounding soft tissue areas, the orbit or the dura, is suspected [11-13]. Gadolinium-enhanced MRI help differentiate tumor from obstructed secretions in paranasal sinuses, determining meningeal and extradural spread and to detect perineural spread [13]. However, MRI is reported to overstage the tumor in many cases [5,12]. The tumor typically shows hypo-intense to intermediate signal in T1 weighted images, whereas the original intensity is increased in T2 weighted images [12,13]. Cystic regions, at the advancing edge, may show hyper-intense regions in T2 weighted images [12,13].

Staging

Kadish et al. were the first researchers to propose a staging classification for olfactory neuroblastoma [14,15]. According to this staging system, the tumors are classified into 4 main types (Table 4): A) when the disease is limited to the nasal cavity; B) when the tumor involves the nasal and paranasal sinuses; C) when the lesion is extended beyond the nasal and paranasal sinuses, involving the cribriform plate, skull base or intracranial cavity. Type D classification is related to metastasis to cervical nodes or distant sites.

Table 3. Diagnostic imaging modalities involved

Imaging modality	*Protocol involved*	*Main findings*
Computed tomography (CT)	Axial/coronal scan, 1-5 mm thick slices, intravenous contrast agent	"Dumbbell-shaped" mass
		Erosion of the lamina papyracea or cribriform plate
		Contrast CT scan usually shows homogeneous lesions with necrotic (non enhancing) areas
Magnetic resonance imaging	with or without contrast	Extent of the tumor to adjacent sites (surrounding soft tissue areas, orbit or dura)
		Differrentiation of tumor from obstructed secretions in paranasal sinuses
		Determining meningeal and/or extradural spread
Magnetic resonance imaging	with gadolinium-enhancement	Detection of perineural spread
		The tumor shows hypo-intense to intermediate signal in T1 images
		The original intensity is increased in T2 weighted images
		Cystic regions may show hyper-intense regions in T2 imaging

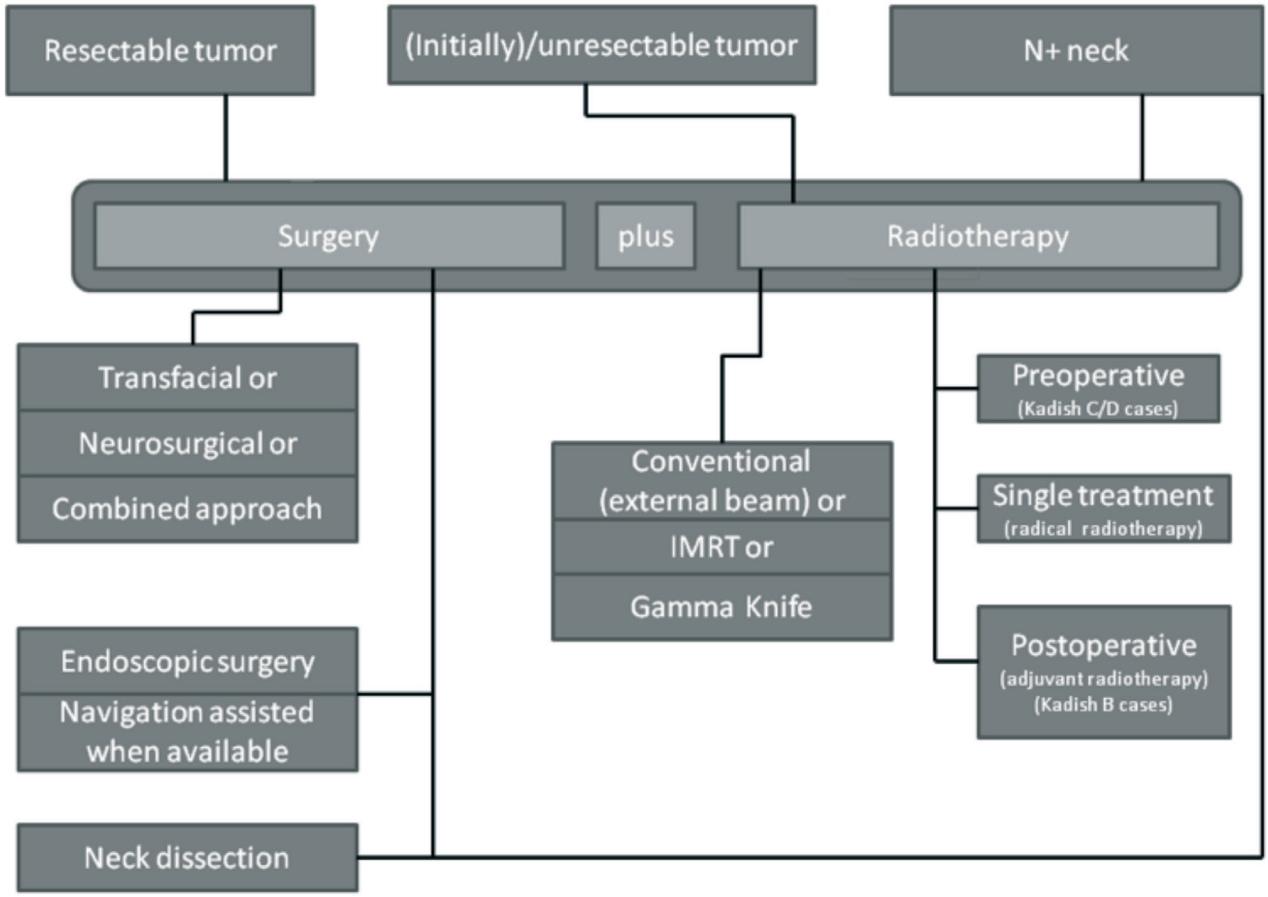

Figure 1. Treatment algorithm for esthesioneuroblastoma.

Various attempts have been made through the years to modify the Kadish's system [5]. Moreover, Dulguerov et al. presented another staging system mainly based on TNM system. This system is apparently taking advantage of the recent advances in imaging, such as computed tomography and magnetic resonance imaging [16,17]. The recently developed Hyams grading system [18] is based on histological findings: grade I classified tumors are well differentiated, whereas grade IV is related to undifferentiated lesions. Several histological parameters, such as preservation of lobular architecture, nuclear polymorphism, mitotic index, tumor necrosis etc are used to document the classification.

Table 4. Staging classification for esthesioneuroblastoma according to Kadish et al.

Type A	Tumor limited to nasal cavity
Type B	Tumor involving nasal cavity and paranasal sinuses
Type C	Tumor invading cribriform plate, skull base or intracranial cavity
Type D	Metastasis to cervical lymph nodes or distant sites

Treatment strategies

As far as the treatment strategies are concerned, combination of surgery and radiotherapy (with or without chemotherapy) is considered to be the standard of care for primary site disease by the majority of researchers (Figure 1) [5]. Such knowledge is mainly based on single institution series (most of them being retrospective studies), as well as on meta-analyses of studies adopting combined treatment modalities. In 2001 Dulguerov et al. reviewed 26 original studies with a total number of 390 cases [17]. They concluded that the combination of surgery and radiotherapy seems to be the optimum approach to treatment: this meta-analysis provides quite adequate evidence that survival rates are significantly improved when surgery plus radiotherapy are involved, compared with surgery or radiation alone. This fact is also supported by two more recent original studies by Gruber et al. [19] and Lund et al. [20]

Combined transfacial and neurosurgical conventional approaches are adopted in several cases, mainly due to the endocranial extension and the close anatomic relationship of esthesioneuroblastomas with the ethmoid roof and cribriform plate [20-22]. The role of open surgery is quite well established through the years and is supported by extended literature. Such approaches usually allow *en bloc* resection of the tumor, ensuring protection of both brain and optic nerve [5,17,22].

On the other hand, the advances in both imaging modalities, endoscopic tools, navigation-assisted surgery and endoscopic surgical techniques have made endoscopic approaches very familiar, as well as considerably feasible for the management of such tumors. Although there are more cases of long-term follow-up in the open surgery groups, it is quite interesting that endoscopic approaches are usually reported to produce equal or better survival rates than open surgery [5,6-8], even when data is stratified for publication year. However, it should be taken into account that tumors treated with open surgery techniques are usually staged as Kadish C and D, whereas endoscopic surgery is more commonly restricted to Kadish A and B lesions [5,22]. Despite this fact, most studies support that endoscopic resection correlates with similar oncologic control rates, compared with conventional open surgery, provided that basic surgical principles with clearance of margins and intradural dissection (when required) are completely maintained 5-7,22,23]. In a recent retrospective multicentre study, Folbe et al. [24] state that properly planned and performed endoscopic surgery could replace craniofacial resection, reporting similar control of the disease and equivalent survival rates. The combination of endoscopic techniques and craniofacial resection is also involved in selected cases [25].

It is quite commonly accepted that neck metastases do not develop for as long as 2 years or more in the majority of the esthesioneuroblastomas [5,26,27]; according to Dulguerov et al. neck metastases are found, by the time of presentation, in only 5% of the patients [16,17].

However, in several different reviews and meta-analyses of the largest and most recent series the overall rate of synchronous and metachronous cervical metastases is reported to range between 20.2 and 23.4% [26-29]. Gore et al. [28] state that 62% of cervical metastases occur 6 or more months after primary treatment. Moreover, the presence of such metastases is usually related to the development of distant metastases and poor prognosis, in general [26,28]. Therefore, the vast majority of the recent studies support that neck metastases should be treated by neck dissection and radiotherapy; in the meta-analysis of Dulguerov et al. survival data demonstrated that only 29% of initially N+ patients were treated successfully, compared with 64% of the N0 patients [17]. This is the reason why most centers advocate the treatment of N+ patients with neck dissection and postoperative radiotherapy [26-29].

Despite the fact that treatment strategy for N+ neck seems to be, more or less, a consensus, based on the current literature, the management of the N0 neck still remains controversial. Although the overall incidence of cervical metastases is reported to be greater than 20%, most surgeons do not advocate elective neck dissection as part of the initial treatment of neck N0 esthesioneuroblastoma cases. This is mainly due to the fact that neck metastases tend to occur quite late in the course of the disease. Therefore, most surgeons prefer to deal with cervical lymph node metastatic disease by the time it is clinically documented [26,28,29].

Radiotherapy alone or more commonly in combination with surgery (or even chemotherapy) is often involved in the treatment plan in the majority of esthesioneuroblastoma cases [30-33]. Most authors support the role of radiotherapy, mainly in cases of incomplete surgical resection or residual disease [30,32].

Conventional radiotherapy usually includes external beam radiation combined with wedge-fields to ensure homogeneous distribution [32-34]. The recommended dose is about 60 Gy [32,33]. Daily intensive – modulated radiation therapy (IMRT), and/or stereotactic radio-surgery (Gamma Knife) are advocated by some authors, especially in cases where critical adjacent sites, such as the optic nerve, the optic chiasm or the brainstem could be at high risk because of the radiation: the tolerance of these anatomical structures is reported to reach a maximum of 54 Gy [35,36]. The results of stereotactic radiosurgery are reported to be very satisfactory compared with those of conventional radiotherapy [35,36]. According to the current literature, adjuvant radiotherapy is usually combined with surgery in Kadish B cases, depending on the degree of histopathologic differentiation. N+ neck, locally invasive and high grade tumors are also considered to be common indications for

postoperative radiotherapy [5,32-34]. On the other hand, preoperative radiotherapy is often involved in advanced disease (Kadish C/D cases) [37].

The efficacy of chemotherapy in treatment protocols still remains unclear. Although esthesioneuroblastoma is classified as a chemosensitive tumor, neoadjuvant chemotherapy alone is not generally recommended [31]. Cisplatin-based chemotherapy regimens are advocated by several researchers, especially in locally or regionally advanced and/or high grade cases [31,38-41]. Hyams' grading is commonly adopted as a significant prognostic factor regarding the tumor's response to chemotherapy [40]. The role of adjuvant chemotherapy is generally not clearly justified.

Given that late local and regional recurrence is considered to be quite common in esthesioneuroblastomas, the need for extended follow up (10, 15 or even up to 20 years after initial treatment) is generally supported by the recent literature [3-5]. Both endoscopic/clinical examination and imaging studies are recommended on a regular basis. The possibility of distant metastases should also be taken into account through the years following initial treatment [3,4].

Conclusions

Olfactory neuroblastoma is an uncommon malignancy of the nasal cavity. The tumor arises from the specialized sensory epithelial olfactory cells comprising about 2-6% of the cases of paranasal sinus and nasal cavity tumors, and 0.3% of upper digestive tract malignancies. Combined surgery and radiotherapy (either conventional external beam or IMRT/ Gamma Knife) are considered to be the standard of care for primary site disease. Elective neck dissection is generally recommended in co-existing nodal disease. Advanced disease, N+ neck, locally invasive and high grade tumors are common indications for postoperative radiotherapy. The role and the efficacy of chemotherapy are still quite unjustified. Multidisciplinary approach of such patients and careful diagnostic and treatment planning on an individual basis are of paramount importance.

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