ORIGINAL ARTICLE

Diagnosis and management of esthesioneuroblastoma

Diagnostic et prise en charge thérapeutique de l'esthésioneuroblastome

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Abstract

Introduction: Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is a rare malignant tumor that develops in the nasal cavity. It accounts for only 1.2% of malignant nasosinus tumor and arises from the olfactory epithelium.
Methods: This retrospective study presents olfactory neuroblastoma cases treated in our ENT department over a period of 36 years, from January 1986 to December 2023.
Results: The study results indicate that the series consisted of 10 cases of olfactory neuroblastoma, with seven females and three males, and a mean age of 40 years. Based on the Kadish classification, 6 cases were classified as stage B, 3 as stage C, and 1 as stage D. Of the 8 patients who underwent surgery, 6 patients also received radiotherapy, while 2 cases were inoperable. After surgery followed by radiotherapy, complete remission was observed in 3 cases. Tumor progression was observed in 2 cases, after 8 and 3 months respectively and tumour recurrence was observed in one patient.
Conclusion: Although the imaging features of olfactory neuroblastoma are non-specific, there are patterns of disease that should strongly suggest and stage this disorder. This is fundamental for surgical planning.

Keywords: Olfactory neuroblastoma, Imaging, Treatment, Prognosis

Résumé

Introduction : L'esthésioneuroblastome (ENB), également appelé neuroblastome olfactif, est une tumeur maligne rare qui se développe dans la cavité nasale. Il représente seulement 1,2 % des tumeurs malignes des sinus et provient de l'épithélium olfactif.
Méthodes : Cette étude rétrospective présente les cas de neuroblastome olfactif traités dans notre service ORL sur une période de 36 ans, de janvier 1986 à décembre 2023.
Résultats : L'étude porte sur 10 cas de neuroblastome olfactif (7 femmes et 3 hommes), d'un âge moyen de 40 ans. Selon la classification de Kadish, 6 cas étaient classés stade B, 3 cas stade C et 1cas stade D.
Parmi les 8 patients opérés, 6 cas ont également reçu une radiothérapie, tandis que 2 cas étaient inopérables. Une rémission complète a été observée chez 3 patients. Une progression tumorale a été observée dans deux cas, après respectivement 3 et 8 mois, et une récidive tumorale chez un patient.
Conclusion : Bien que les caractéristiques d'imagerie du neuroblastome olfactif soient non spécifiques, certains aspects de la maladie doivent fortement évoquer ce diagnostic et permettre d'en déterminer le stade. Ceci est fondamental pour la planification chirurgicale.

Mots-clés : Neuroblastome olfactif, Imagerie, Traitement, Pronostic.

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Introduction

Sino-nasal cancers are often considered a group of indistinguishable lesions due to their late detection and difficulty in determining their initial location. Moreover, they have features that differentiate them from other cancers of the upper aerodigestive tract. Esthesioneuroblastoma accounts for 3 to 6% of all such tumors [1]. Since Berger and Luc´s initial description of this rare neoplasm in 1924, the literature has documented approximately 1200 cases of ENB. A tumor can develop from the olfactory epithelium and often presents with rhinological signs. Other ocular or neurological signs may be primary or secondary [2]. Imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are used to provide a precise locoregional assessment. CT is the preferred test for providing an anatomical analysis of the naso-sinus cavities. It determines the size, topography, and extension to adjacent structures, as well as assesses the extent of bone destruction. MRI provides a precise analysis of the contents of the nasal-sinus cavities and their relationship to the meninges and brain [3,4]. The combination of CT and MRI allows for accurate preoperative evaluation. Kadish [5] proposed a classification to guide therapeutic management based on anatomopathological evaluation. Treatment typically involves surgery and radiotherapy [6]. This report presents our institution's experience and compares it with a literature review.

Methods

This is a retrospective study of 10 patients with ENB collected from our ENT Department over a period of 36 years, from January 1986 to December 2023.

The tumors were classified using the Kadish classification [5]. The tumors are classified into four stages based on their location and extent. Stage A tumors are located in the nasal cavity, stage B tumors extend into the paranasal sinuses, stage C tumors extended beyond the paranasal sinuses, and stage D tumors involve the cervical lymph nodes and/or distant metastases.

Dulgnerov [6] proposes a four-stage system for tumors in the nasal cavity and paranasal sinuses. T1 refers to a tumor that has developed in the nasal cavity and paranasal sinuses, leaving a space between the tumor and the septum. T2 refers to a tumor that has developed in the nasal cavity or paranasal sinus and is in contact with the septum and/or extends to the sphenoid bone. T3 refers to a tumor that involves orbit or is extradural intracranial. T4 refers to a tumor that is intradural intracranial.

The anatomopathological examination of biopsies and surgical specimens in our series used the Hyams grading system. The tumors are classified into low-grade (I and II) and high-grade (III and IV) categories, and is used to evaluate the prognosis [7].

Results

The series includes 10 cases of ENB, with seven females and three males, and a mean age of 40 years (range: 11-77 years). All cases presented with rhinosinusitis, with associated ophthalmological signs in 30% of cases and neurological signs in 30% of cases, indicating locoregional tumor extension. One case presented with a syndrome of inappropriate secretion of ADH (SIADH).

Tumor formation was observed in all cases. Three cases demonstrated complete filling of the nasal cavity, while two cases exhibited deviation of the nasal septum to the contralateral side.

The tumor lesion was polyploid, with a variable color ranging from red to grey, often hemorrhagic, and occasionally with superficial ulceration. None of the cases presented cervical adenopathy. Exophthalmos was observed in two patients, and only one case had limited visual acuity, which was restricted to light perception. All patients underwent a fundoscopic examination which revealed a pathologic finding in only one case, where the retina appeared greyish. Neurological examination showed ophthalmoplegia in one case, hemianopsia in another, and trismus in a third.

CT scans of the head and face were performed on all cases, and the findings are summarized in Table 1 (Table 1).

Table 1. CT findings in our series

Features	Number	Percentage (%)
Unilaterality	10	100
Bony lysis of the lamina papyricea	4	40
Bony lysis of the inter sinus nasal septum	3	30
Cribriform plate lysis	3	30
Intra-tumoral calcifications	4	40
Extension to the paranasal sinuses	10	100
Extension to the orbit	4	40
Extension to the cavum	0	0
Extension to the infratemporal fossa	1	10
Endocranial extension	2	20
Heterogeneity	10	100
Enhancement after contrast injection	10	100

All cases presented with unilateral tumor lesions, with bone lysis in nine cases, sinus extension in all cases, orbital extension in four cases, and endocranial extension in two cases (Fig. 1).

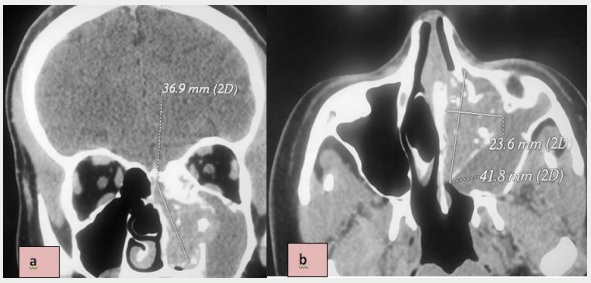

Figure 1. CT scan of the facial mass in the parenchymal window, coronal section (a) and axial section (b) showing a nasosinusal tumour formation with calcifications extending into the maxillary sinus and homolateral ethmoid cells in contact with the lamina papyricea and roof of the ethmoid.

MRI was performed in six cases, which revealed that the tumor was T1 hypointense in four cases and T1 isointense in two cases. In all six cases, it was T2 hyperintense and highly gadolinium-enhancing.

The MRI revealed orbital extension in three cases, one of which had fat and muscle extension, and endocranial extension in two cases.

The tumor was classified as Kadish stage B in six cases, stage C in three cases, and stage D in one case due to pulmonary metastases (Fig. 2). Only one case had pulmonary metastases.

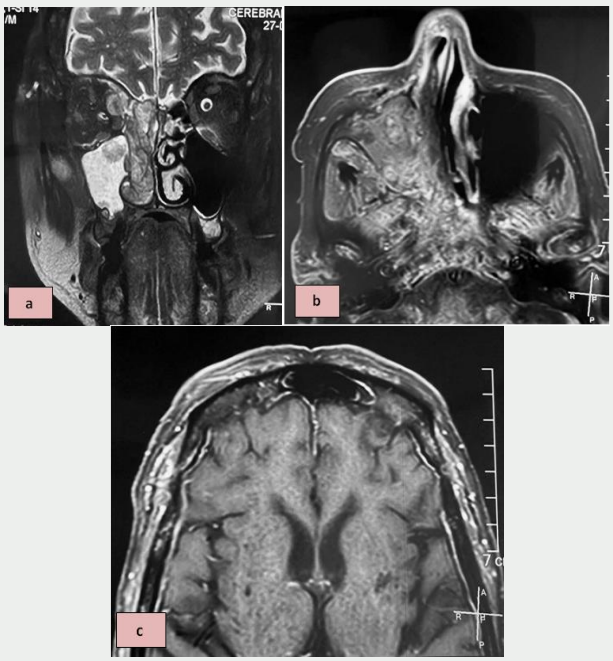

Figure 2(a,b,c). MRI of the facial bone in coronal section in T2 (a) and axial T1 (b,c) sequences showing a tissue process in T2 isosignal in the right nasoethmoidal region with extension to the maxilla (a), right infra-temporal fossa (b) and bifrontal endocranium (c).

The diagnosis of olfactory ENB was based solely on anatomopathological examination of the biopsy specimens. Hayms histological grading was used in all cases. Two patients were classified according to their grade: one as grade, five as grade 2, two as grade 3, and one as grade 4 (Fig. 3, 4,5).

The therapeutic decision was made during a multidisciplinary consultation. External surgery was performed in seven cases, with the Moure para latero nasal approach (MPA) used in six cases and the Rouge Denker approach in one case. The endonasal route was only used in one case, as the other cases were from the 1990s. The procedure included a midline meatotomy, ethmoidectomy, and sphenoidotomy, which was carcinogenic. In one case involving the orbit (fat and orbital muscle), the patient declined exenteration. (Table 2).

Postoperative radiotherapy was administered in six cases. A dose of approximately 65 Gy was prescribed for tumors and lymph nodes classified as Kadish stage B and C. Radiotherapy was only recommended postoperatively, with no cases undergoing radiotherapy exclusively for curative or palliative purposes.

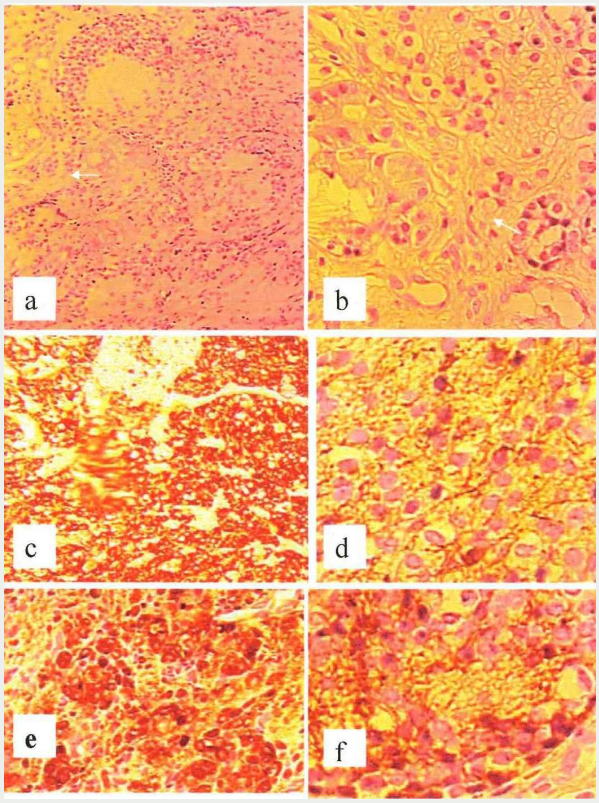

Figure 3. Esthesioneuroblastoma grade II

a+b Tumour proliferation with fairly monomorphic round cells grouped in rosettes in an abundant fibrillar background.

c: Positive staining with anti-protein S-100 antibody

d: positive staining with anti-NF antibody

e: positive staining with anti-NSE antibody

f: positive labelling with anti-synaptophysin antibody

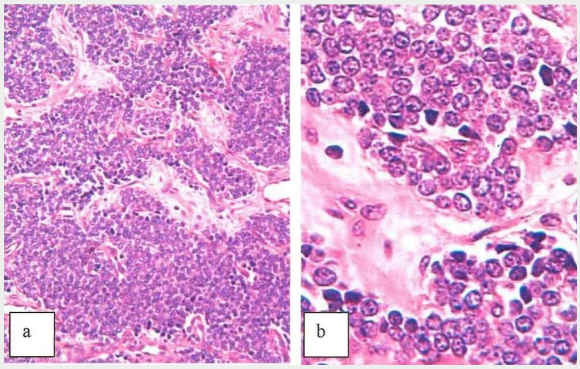

Figure 4. Esthesioneuroblastoma grade III

(a+b): (HEx200/HEx400): Proliferation of malignant round cells with numerous mitoses arranged in clusters. The stroma is sparsely fibrillated.

Chemotherapy was recommended for patients with lung metastases. Unfortunately, the patient passed away before treatment. One patient was considered inoperable due to the extent of the tumor, which precluded surgery, and their very poor general condition, which precluded any palliative treatment.

Post-operative CT scans were performed on six patients, on average four months after surgery. In one case, the patient did not seek post-operative care until two years later and a CT scan was performed at that time. The CT

scan revealed signs of tumor recurrence in two cases. In the first case, it showed extension into the orbit, frontal sinus, and anterior floor of the brain, compressing the lateral ventricular frontal horns and the brain scythe. The second case showed a recurrence of the nasal tumor without orbital or endocranial extension. Three patients were lost to follow-up. Complete remission was observed in three cases after MPA surgery followed by postoperative radiotherapy. The follow-up period was 9, 8, and 7 years, respectively.

The evolution for these cases was as follow: Progression continued in two cases after eight and three months, respectively. The first case had undergone Rouge Denker surgery for Kadish stage B, followed by postoperative radiotherapy. The second case had undergone MPA surgery initially, and exenteration was initially refused despite large tumor margins in the orbit. The progression was extensive, affecting the orbit and endocranium. The patient underwent then combined surgery involving exenteration and prosthesis placement.

In one case, tumor recurrence was observed two years after surgery. However, the patient was lost to follow-up before receiving post-operative radiotherapy. The same approach was used upon the patient´s rediscovery, and post-operative radiotherapy was administered.

Three patients were lost to follow-up: the first patient was considered beyond treatment, the second patient was lost to follow-up after surgery and the last one was lost to follow-up after completing post-operative radiotherapy. One patient died before receiving chemotherapy.

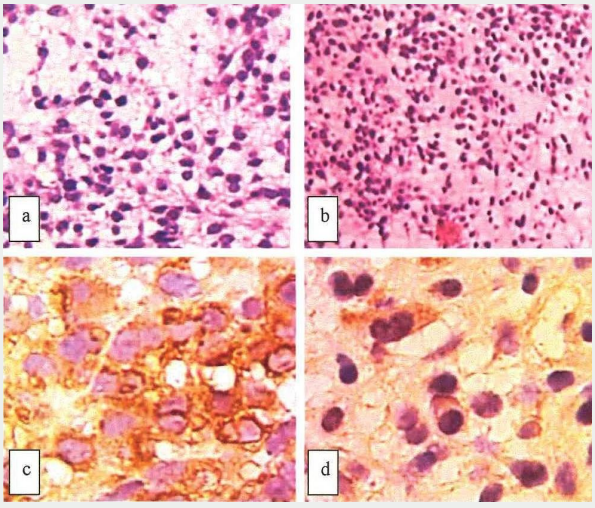

Figure 5. Esthesioneuroblastoma grade I

(a+b): (HEx200/HEx400): Proliferation of malignant cells with low cellular pleomorphism

and mitosis in an abundant fibrillar matrix.

c: Positive staining with anti-protein S-100 antibody

d: positive for anti-GF AP labelling

Table 2. Surgical approaches according to the extent of tumour involvement

Observation /year	Extent of lesion	Kadish stage	Surgical approach	Exeresis limit
1 (1994)	Ethmoidonasal/ Lysis of intersinuso-nasal septum	B	MPA	negative margins
2 (2001)	Ethmoidonasal/ maxillary sinus/orbital lamina papyricea	B	MPA	Tumoral
3(2001)	Nasal fossa/maxillary sinus	B	Rouge Denker	Negative margins
4(2006)	Ethmoidonasal/ papyraceous lamina/ CISN/ orbit (fat and muscle intact)	C	MPA (in contact with the eyeball)	Tumoral
5(2006)	Ethmoido-nasal	B	MPA	Negative margins
6(2010)	Ethmoido-nasal	B	MPA	Negative margins
7(2018)	Ethmoid-nasal, maxillary sinus, papyraceous lamina, orbit (fat and muscle intact)	C	MPA	Negative margins
8 (2020)	Ethmoido-nasal, maxillary sinus	B	Endonasal	Negative margins

Discussion

Olfactory ENB is a rare tumor of the nasal sinus tract that develops at the expense of the olfactory neuroepithelium. It accounts for 1.2% of all malignant nasal tumors and 3 to 6% of all nasal tumors. The disease can affect both sexes, although some authors report a slight female predominance. Incidence occurs at any age, but there are two peaks: between the ages of 10 and 20, and between the ages of 50 and 60 [6,8,9].

The literature has not identified any clear risk factors [10]. However, some studies suggest a possible association with nitrosamines, wood dust, and certain genetic abnormalities [2,9].

Clinical manifestations at diagnosis are non-specific and depend on local or regional tumor extension [2,11,12]. ENB is an unifocal tumor and symptoms are often unilateral [6]. In 75% of cases, rhinological signs, mainly nasal obstruction and epistaxis detect the tumor [3,9]. Anosmia or rhinorrhea may also be present. Ophthalmological involvement including orbital invasion, is observed in 20 to 30% of cases, resulting in exophthalmos, visual disturbances, and even ophthalmoplegia. The presence of ocular signs indicates an advanced stage of the disease [3,6].

Patients may also present with facial pain or headache, which could indicate the presence of a paranasal sinus tumor, irritation of the branches of the trigeminal nerve or, exceptionally, meningeal irritation due to intracranial tumor invasion [6].

In our series, recurrent epistaxis was the most common symptom, observed in 6 patients (60%), followed by hyposmia in 3 patients (30%). Ophthalmological signs were present in 3 of our patients (30% of cases).

Symptoms of ENB may be associated with cervical swelling and/or a paraneoplastic syndrome, such as Cushing's

syndrome, malignant hypercalcemia, or hyponatremia due to SIADH [3,6,9]. This confirms the endocrine nature of the tumor. Our series included one case of SIADH.

On endoscopy, the tumor appears as a polypoid formation in the nasal cavity, varying from grey to dark red. It is obstructive, friable, and bleeds on contact [6,9].

Imaging, including both CT and MRI, plays a crucial key role in accurately staging ENB. To ensure a precise assessment of the disease extent, it is essential to include these imaging modalities [13].

The combination of CT and MRI provides an accurate assessment of tumor extension. CT is essential and systematic in all patients and is part of the preoperative evaluation [10,13]. A CT scan reveals a hypodense mass with fine intra-tumoral calcifications [1,3,6,10]. At different stages, the mass has the potential to damage nearby bony structures, such as the cribriform plate, the roof of the ethmoid, and the medial wall of the orbit [2,10,13].

The tumor is globally enhanced on sections of the injected parenchymal window, with hypodense areas corresponding to areas of necrosis. Unilaterality and osteolysis are considered criteria for malignancy. Bone lysis may involve the inner wall of the orbit, the inter-sinus-nasal septum, and rarely the cribriform plate of the ethmoid [2,13]. CT is essential for assessing the tumor and its local invasion of surrounding bony structures [13]. CT scans were performed in all cases in our series to evaluate regional spread to the cervical lymph nodes and distant metastases. Intra-tumor calcifications were found in three cases. Additionally, there were three cases of intracranial invasion, two primary and one secondary, without clinical neurological manifestations. The tumor appears hypo- or iso-signal with a clear hypo-signal in areas of necrosis on T1-weighted MRI. On T2-weight MRI, the tumor appears iso- or hypersignal and is clearly enhanced by gadolinium injection [6,13].

Various studies have shown that the radiological appearance of ENB (MRI and CT) lacks specificity and shares similarities in signal and density with other neoplasms of the nasal cavity. It is important to note that these findings are not specific to ENB and can be observed in other neoplasms of the nasal cavity as well. ENB most typically originates from the roof of the unilateral nasal cavity in the cribriform plate or above the middle turbinates. Although less common, ENB can also originate from the sellar region, parasellar region, nasopharynx, maxilla, and sphenoid sinuses. However, our study did not observe these sites [10]. Calcifications and cysts along the intracranial tumor margin are considered pathognomonic for ENB, as reported in previous studies [10,11,13,14,15]. In our study, calcifications were found in four cases.

Ouskian et al recommend performing an MRI in addition to a CT scan in cases where nasal roof erosion with intracranial extension is shown, as it provides a better study of intracranial lesions [16]. MRI can improve the preoperative assessment of tumors by identifying any intracranial or intraorbital extension suspected on CT, particularly in cases of bone lysis [1,3,6].

It is a highly accurate method for assessing subtle orbital and intracranial invasion, including rare subarachnoid seeding. The use of fat-saturated MRI sequences can aid in distinguishing tumor from fat and orbital muscle. The appearance of the tumor-fat interface can indicate whether the lesion is contained by the periorbital fascia, or if there is open orbital invasion [13]. Imaging techniques are useful in accurately assessing perineural spread of the tumor and distinguishing between dural and parenchymal involvement.

However, surgery is required to diagnose dural and periorbital invasion [13].

Furthermore, T1 gadolinium sequences can differentiate between sinus retention caused by tumor obstruction, which is not enhanced, and the tumor itself, which is hypersignal [13].

In our study, we performed MRI on six patients whose tumor boundaries were more extensive than initially judged on CT. Imaging can be used to assess the staging of ENB and provide information on the extent of the tumour. Kadish proposed a four-stage clinical classification based on the tumor's extension [4]. Dulgnerov and other teams proposed a more precise classification based on the TNM classification, using CT and MRI to determine extension [7]. The study classified 6 cases as stage B, 3 cases as stage C, and 1 case as stage D. Imaging is also used to exclude differential diagnoses, such as meningocele, meningoencephalocele, and hyper vascular tumors, such as nasopharyngeal fibroids [12].

Clinical assessment, cervical MRI/CT, and PET-FDG (fluorodeoxyglucose positron emission tomography) are necessary to evaluate cervical extension. PET scans can detect cervical adenopathy not visible on CT scans in nearly 20% of cases [6].

Whole-body PET/CT provides a comprehensive analysis of neck and distant lymph node metastases. PET/CT has the added advantage of displaying metabolic activity in lymph nodes that are not pathologically enlarged or abnormally enhanced on MRI.

Furthermore, PET/CT can demonstrate reactive sclerosis and bone remodeling, which are not well-assessed by MRI [16]. The distant metastases most commonly occur in the lungs, liver, and bones. According to the pooled data, 12% of patients developed distant metastatic disease. The 6-month overall survival rate after diagnosis of distant metastasis was reported to be 63% [10,13].

As part of the extension assessment, it is recommended to undergo a thoraco-abdominal CT scan and/or abdominal ultrasound [6]. In our study, only one case of distant metastasis was identified during the extension work-up.

Histology confirmed the diagnosis of ENB on imaging [3]. The Hyams four-tier grading system for ENB, is based on tumor architecture, mitotic activity, nuclear pleomorphism, abundance of fibrillar matrix, presence of rosettes, and necrosis [17].

Therapeutic decisions for ENB, due to its rarity, rely mainly on the analysis of published cases [12].

There is no standard treatment for tumors of this type. Determining the optimal therapeutic approach is challenging due to the limited number of patients treated at a single centre and the fact that these cases are spread over time, often spanning more than 20 years, resulting in varied outcomes [12].

The surgical technique used depends on the initial stage of

the tumor. Historically, craniofacial resection has been the preferred operation. This involves a bifrontal craniotomy to remove the cribriform plate, crista galli, adjacent dura mater, and olfactory bulbs and tracts in bloc [10].

For localiszed tumors, a transfacial approach with para latero nasal rhinotomy has been proposed. However, the development of endoscopic surgery over the last decade has led to comparable carcinological outcomes with limited surgical morbidity and hospital stay. This is particularly true for Kadish stages A and B [18,19].

For locally advanced tumors (invasion of the orbit or anterior fossa), a mixed surgical approach is preferred. This can be either trans-facial or endoscopic and neurosurgical [10].

When evaluating trials comparing endoscopic and open approaches, it is important to consider several factors. The choice of surgical approach for treating nasal tumor may be influenced by the patient's condition, with more advanced Kadish stages typically treated with an open approach and less extensive lesions potentially favoring an endoscopic approach. However, this introduces a potential bias as the Kadish stage is just one of several important prognostic factors. Additionally, the Kadish staging system does not consider other factors such as skin or orbital erosion/intraconal extension, which may require open approaches [6].

Furthermore, it is worth noting that most endoscopic case series are recent, as this approach has only recently been introduced. A follow-up times are shorter and survival rate may change over time due to the recent introduction of this approach, resulting in a shorter follow-up time and the possibility of changes in survival rates over time. However, several series have demonstrated positive outcomes and negative surgical margins when the endoscopic approach is used early on [20,21]. It is important to keep in mind the following caveats.

For unresectable tumors, treatment usually involves a multimodal approach that combines chemotherapy and radiation therapy, possibly followed by craniofacial surgery [18].

Although some centers recommend preoperative radiation therapy, it is not yet a standard procedure [19]. Radiotherapy targets both the tumor bed and the lymph nodes, with the radiation dose ranging from 45 to 60 Gy in the case of a large tumor volume [22].

Conclusion

ENB is a rare form of cancer that presents a variety of clinical symptoms and signs. Patients with ENB often present with advanced disease and significant local invasion due to the subtle nature of the symptoms. Although the imaging features of ENB are non-specific, certain disease patterns suggest the diagnosis. CT and MRI are essential for assessing the extent of the disease before surgery.

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