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Esthesioneuroblastoma: A Rare and Aggressive Sinonasal Tumor – Case Series and Review of the Literature

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Abstract **Original Research Article**

Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma, is a rare malignant neuroepithelial tumour of the nasal cavity. Its presentation is often non-specific, dominated by nasal obstruction, epistaxis or hyposmia, sometimes associated with ophthalmological or neurological signs, which explains why diagnosis is often delayed. Histologically, it is a proliferation of small, undifferentiated round cells, confirmed by immunohistochemistry. The most commonly used classification system for staging is the Kadish classification. This tumour is locally aggressive and characterised by a high risk of recurrence, sometimes late. The standard treatment is complete surgical excision followed by radiotherapy, while the role of chemotherapy remains controversial. Recent advances in radiotherapy and the adoption of endoscopic approaches offer hope for better local control with reduced morbidity. However, the prognosis remains uncertain, highlighting the importance of early diagnosis, prolonged follow-up and multidisciplinary management in specialised centres.

Keywords: Esthesioneuroblastoma, Olfactory neuroblastoma, Sinonasal tumor, Kadish staging, Surgery, Radiotherapy, Chemotherapy, Prognosis.

INTRODUCTION

Esthesioneuroblastoma (ENB), also referred to as olfactory neuroblastoma, is a rare malignant tumor that comes from the olfactory epithelium of the nasal cavity, indeed, only approximately 300 cases had been reported between 1924 and 1989. At first, it was described by Berger *et al.,* in 1924 as "esthesioneuroepitheliome olfactif"[1] and accounts for approximately 5 to 6% of all malignant sinonasal tumors [2].

ENB isn't age related, it can occur at any age with a bimodal incidence peak reported in the second and sixth decades of life [3-5]. Its clinical presentation is often nonspecific, typically including unilateral nasal obstruction, epistaxis, or hyposmia, which may lead to delayed diagnosis.

This tumor is diagnosed mainly by imaging, especially MRI in the first place, but also by histopathological examination supported by immunohistochemistry. Regarding its biological behavior, it is variable. Some patients follow a slow, indolent course while others show a rapid progression with potential for local invasion and distant metastasis.[2,6]

The most common treatment of ENB consists of craniofacial surgical resection followed by adjuvant radiotherapy. but minimally invasive endoscopic approaches are increasingly adopted in early-stage disease, with promising oncological outcomes [7].

Due to its rarity, available clinical data are limited and largely based on retrospective studies or small case series. In this context, we present a series of six patients with esthesioneuroblastoma managed in our department, describing their clinical, radiological, therapeutic, and follow-up characteristics, in comparison with findings reported in the literature.

MATERIEL AND METHODS

We conducted a retrospective descriptive study on patients diagnosed with esthesioneuroblastoma and managed in the Radiation Oncology Department of

Mohammed VI University Hospital in Marrakech, over a nine-year period from April 2016 to June 2025.

The study included all patients with histologically confirmed esthesioneuroblastoma treated in our department during the study period. Patients with incomplete or non-exploitable medical records were excluded.

Data was collected from hospitalization registers, electronic medical records, and radiotherapy software. The variables analyzed included epidemiological data (age, geographic origin, socioeconomic level, risk factors), clinical features, paraclinical findings, therapeutic approaches, and patient outcomes. All data were recorded on a standardized data collection form.

All patients were regularly followed up to assess treatment response, recurrence, and survival. Data collection was conducted in compliance with institutional ethical standards

RESULTS

A total of six patients with histologically confirmed esthesioneuroblastoma were included in this study, representing 11.4% of all sinonasal tumors treated at our department between 2016 and 2025. The study included four males and two females, with a mean age of 23.1 years (range: 6–56 years). No risk factor was clearly identified. The mean consultation delay was 3.5 months, ranging from 1 to 9 months

The most common grounds of consultation were sinonasal symptoms such as unilateral nasal obstruction, epistaxis and hyposmia that were present in all our patients. (see table No1)

Neurological symptoms were present in 83% of patients, including facial pain (n=3) and signs of intracranial hypertension (n=1). Ophthalmological signs such as exophthalmos, tearing, and decreased visual acuity were also observed. In addition, two patients had cervical lymphadenopathy at diagnosis.

Table 1: Symptoms

Cheek swelling	**3**	**50%**
Nasal obstruction	5	83%
Epistaxis	3	50%
Eyelid edema	1	17%
General health impairment	5	83%
Lymph node syndrome	2	33%
Visual disturbances	1	17%
Tearing (epiphora)	2	33%
Intracranial hypertension syndrome	2	33%
Facial pain	4	66%
Exophthalmos	2	33%
Vomiting	1	17%

Nasal endoscopy, sinus scan and face MRI were the most common radiological examinations of 100%, 66% and 66 in the same order, other complimentary examinations were demanded; cerebral CT and cerebral MRI of 33% each.

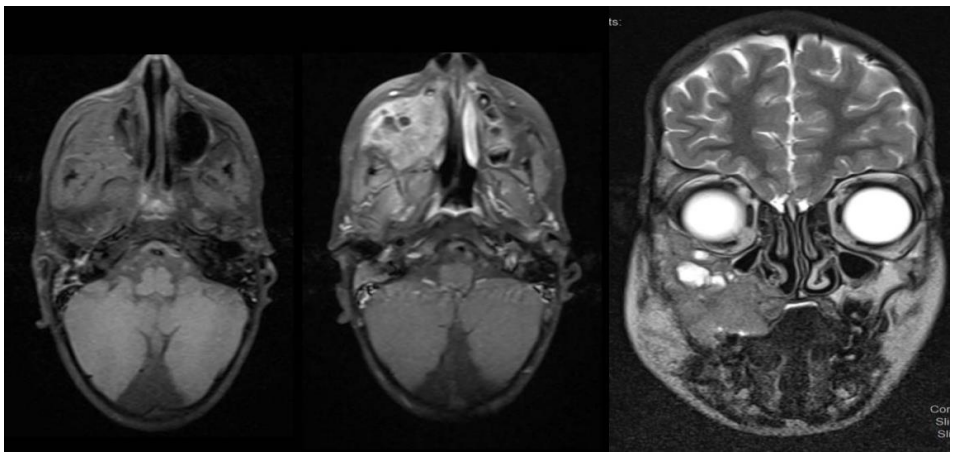

Figure 1: Brain MRI of child showing axial T1, T1 with Gadolinium, and coronal T2 sections demonstrating a tumoral process centered on the right maxillary sinus with local extension

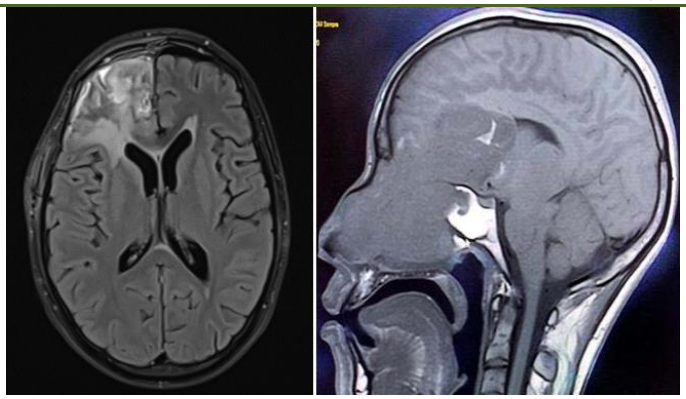

Figure 2: Brain MRI T2-FLAIR sequences in axial and sagittal planes showing a midfacial lesion centered on the ethmoid with intracranial extension

Following the results of the physical and radiological examinations, The Kadish classification modified by Madira gave the following results: five patients (83.3%) were stage C and one patient (16.7%) was stage D.

All the diagnosis were confirmed by an anatomo-pathologic examination that showed tumor proliferation with round undifferentiated cells with necrosis for 3 patients and without for the rest. The immuno-histochemical examination, the only antibody done to all the cases was positive in 80%.

Locoregional imaging assessment was performed using facial MRI in 83% of cases and facial CT in 60%. Distant staging included thoracic CT in all cases, abdominopelvic CT in 66%, and abdominal ultrasound in 33%.

Surgical treatment was carried out in 66% of patients, using various approaches including segmental nasomaxillary maxillectomy, a two-stage procedure combining craniotomy and transfacial resection, and endoscopic resection with ethmoidectomy and sphenoidal/pterygoid extension removal.

Radiotherapy was delivered in five cases: as adjuvant therapy in three, as exclusive treatment in two, and for spinal cord decompression in one palliative case. The total dose ranged from 30 to 66 Gy, administered in 10 to 33 fractions of 2 to 3 Gy. The last patient just got out of surgery and has radiotherapy planned but he beneficiated from embolisation pre-operatoire

five patients received chemotherapy. Three were treated with etoposide–cisplatin, one with doxorubicin–vincristine–etoposide, and one pediatric patient with the HR-NBL-M10 protocol. Chemotherapy was given as neoadjuvant treatment in four cases, adjuvant in two, and concomitant in one

The overall outcome was poor. All the patients developed locoregional or metastatic recurrences for which they received palliative care.,

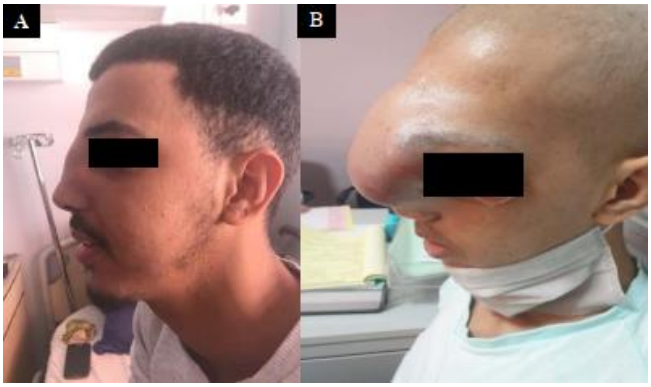

Figure 3: Profile picture of patient after the third cycle of chemotherapy (A) and at the time of recurrence (B) The mean overall survival was 15.4 months, ranging from 9 to 26 months

DISCUSSION

Malignant sinonasal tumors are rare, with esthesioneuroblastoma (ENB) accounting for only 3–5% of cases; approximately 1,500 cases have been reported worldwide [8]. The increase in published cases in recent years reflects improved diagnostic capacity rather than a true rise in incidence. Epidemiological analyses, including the one of Broich et al. (747 cases), show no major sex difference, although a slight male predominance has been noted (55% vs. 45%) [2]. ENB can occur at any age, with a bimodal distribution peaking

in the 2nd and 4th–5th decades [8]. More recent studies report cases from 18 months to 85 years, with a predominance in the 5th–6th decades [9,10].

Clinically, the diagnostic delay ranges from 1 to 4 months with an average of 2.4 months, often shorter than in other regional series, explained by early, disabling symptoms [11,12] (Rhinonasal signs are most frequent, present in 75% of cases, including nasal obstruction (53–100%), epistaxis (10–52%), and hyposmia/anosmia (6–35%) [13]. Neurological signs such as facial pain, intracranial hypertension (headache, vomiting), or rarely seizures and SIADH may occur [13]. Ophthalmologic involvement is reported in up to 20% of cases [12,13], including decreased visual acuity, diplopia, lacrimal obstruction, or exophthalmos. Cervical nodal metastases are observed in about 20% of patients [14], while distant metastases occur in 6–40%, most often pulmonary, osseous, or less frequently neurological [15]

Diagnostic work-up relies on CT for initial assessment by providing information regarding bony erosion and MRI for locoregional extension evaluation, particularly towards the skull base and into soft tissue including dura and brain. It provides better discrimination between the tumor and nasal secretions, as well as a more accurate assessment of the orbit and intracranial structures.The contribution of MRI has been crucial in improving the preoperative evaluation of these tumors, allowing a more precise characterization of possible intracranial or intraorbital extensions suspected on CT analysis, especially in cases of bone lysis [16-20].

More recently, the addition of positron-emission tomography (PET) scanning has been recommended, both for staging and restaging. A retrospective review of 77 PET/CT scans in 28 patients found that 36% of patients were upstaged on the basis of the PET/CT.[21] Endoscopic examination is essential for evaluating the extent of the tumor and for obtaining a biopsy specimen.

Most olfactory neuroblastomas arise in the superior nasal cavity and are intimately related to the cribriform niche through which they readily spread macroscopically and microscopically to involve the olfactory bulbs and tracts. This spread may not be apparent, even on detailed imaging, and may only be confirmed on subsequent histological examination[8]

Histological diagnosis of olfactory neuroblastoma requires expertise as it may not be easily distinguished from other sinonasal tumors, including neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, melanoma, lymphoma, plasmacytoma, embryonal rhabdomyosarcoma, Ewing sarcoma, and primitive neuroectoderma tumors.[5]

The typical histologic appearance of an olfactory neuroblastoma includes the presence of characteristic cells separated into nests or compartments by fibrovascular septae, neurofibrillary interce llular matrices, and rosette format ions [22]

Immunohistochemical and ultrastructural investigations are therefore required for diagnosis.[23]Olfactory neuroblastomas are usually positive for S-100 protein, chromogranin, and synaptophysin.[24,25]

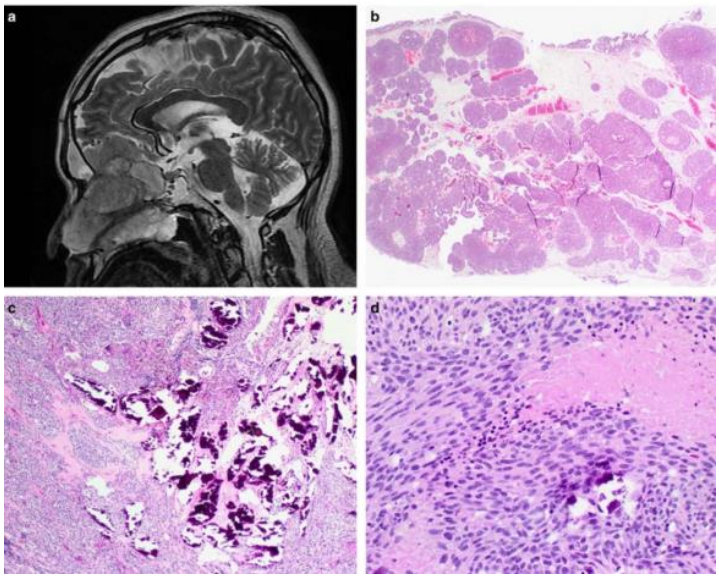

Figure 4 : Aggressive tumor of the nasal cavity with intracranial extension on T2-weighted MRI (a). A lobular architecture is almost always present (b). Calcifications may be observed (c). Tumor necrosis (d) and increased mitotic activity are generally seen in higher-grade tumors[26]

The Hyams classification (grades I through IV) is based on histologic differentiation; the grade IV designation is used to describe undifferentiated sinonasal carcinomas. [22]

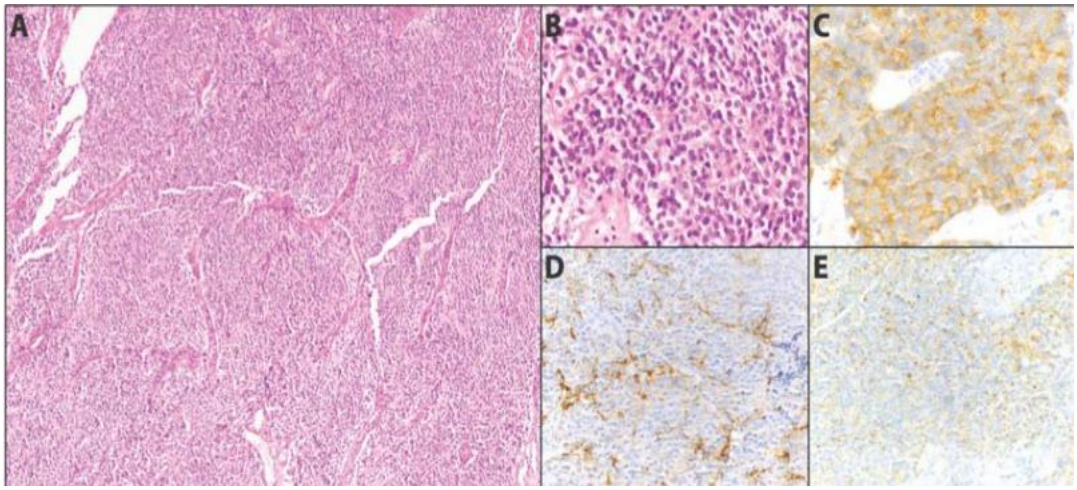

Figure 5: Tumor cells identified with neuron-specific enolase (A, B), synaptophysin (C), S-100 protein (D), and chromogranin (E)

Because malignant lesions of the nasal cavity are so rare and because many different histologic types of tumors abound, no approved classification and staging system has been universally accepted. but stage at presentation has been shown to be highly predictive of survival.[3,27]

In fact, the more well accepted staging is the Kadish classification system (stages A through C) who was the first to propose a staging classification for ONB, [28] which is based on the clinical spread of the tumor; stage A tumors are confined to the nasal cavity, stage B lesions involve the sinuses; and stage C masses involve the midd le cranial fossa and the retrobulbar orbit." Which was later modified by Morita to include stage D (nodal/distant metastases), while Dulguerov proposed a TNM system, though with limited prognostic validation [4,29].

According to the meta-analysis by Marinelli *et al.,* (678 patients), metastatic spread occurred in 6% of cases, usually at a late stage in the disease course, with a mean onset of 15 months after initial diagnosis [15]. However, other series have reported higher rates ranging from 30% to 40% [30]. The most common metastatic sites are lymph nodes, lungs, and bones, with less frequent neurological involvement. In our series, 3 out of 5 patients developed metastases within a maximum period of 13 months, with a mean of 6.5 months. Distant staging primarily relies on chest CT, considered the gold standard, while abdominal ultrasound is useful for detecting hepatic or nodal metastases. However, its diagnostic value may be limited by obesity or bowel gas, requiring an abdominal CT in case of uncertainty [31]. Finally, depending on clinical presentation, further investigations such as brain MRI, bone scintigraphy, spinal MRI, or PET scan may be indicated.

Management of esthesioneuroblastoma is based on a multimodal strategy combining surgery, radiotherapy, and chemotherapy.

Surgical resection is considered the treatment of choice for esthesioneuroblastoma. The gold standard is *complete excision via craniofacial resection (CFR)*, introduced in 1976 at the University of Virginia by Jane and Fitz Hugh. This approach allows en bloc resection of the tumor, including the ipsilateral cribriform plate and crista galli.[32] It often requires a multidisciplinary strategy involving otorhinolaryngology, neurosurgery, as well as plastic and maxillofacial surgery.

Due to the close anatomical relationships of the tumor with the orbit and the anterior skull base, achieving clear surgical margins is often challenging. Preservation of these structures when uninvolved, or their resection in case of invasion, further complicates the surgical procedure[10]

The adoption of CFR significantly improved survival (from 37.5% to 82%) and reduced recurrence rates (from 60% to 40%) in some series. However, it remains associated with considerable morbidity and mortality [6].

More recently, purely endoscopic resections, or combined endoscopic–open approaches, have gained popularity, especially for tumors with minimal or no intracranial extension [3].

A meta-analysis of 361 patients reported superior survival with endoscopic versus open surgery [33] However, this apparent advantage may reflect selection bias due to uneven tumor stage distribution between treatment groups(as advanced tumors (Kadish C–D) are generally treated by open CFR) [34].

Overall, the literature suggests that endoscopic resections may be appropriate for limited tumors (Kadish A–B), whereas advanced stages (Kadish C–D) are better managed with craniofacial approaches.

Surgical resection, whether open or endoscopic, should aim for en bloc removal with negative margins. Positive margins are considered an adverse prognostic factor, although their impact may be mitigated by adjuvant radiotherapy [27,35]

RADIOTHERAPY

Although no high-level evidence is available, adjuvant radiotherapy is currently considered the standard of approach after surgery for esthesioneuroblastoma, regardless of resection completeness. Retrospective studies consistently demonstrate improved local control with adjuvant radiotherapy, with significantly higher recurrence-free survival rates when combined with surgery compared to either modality alone. [35] Nevertheless, no long-term overall survival benefit has been established.[36,37] Exclusive radiotherapy should only be considered in cases of absolute surgical contraindication, as both local control and disease-specific survival are markedly inferior. [38] Analysis of the SEER database reported a mean disease-specific survival of 92.8 months with radiotherapy alone versus 216.8 months with combined treatment. Standard postoperative three-field radiotherapy is usually given to a dose of 55 Gy to 65 Gy [3].

Preoperative chemoradiation (50–60 Gy with cisplatin–etoposide) has shown promising complete pathological responses in Kadish C tumors, though associated with significant toxicity.[39] Advances in technique have shifted practice toward intensity-modulated radiotherapy (IMRT), preferred over 3D conformal radiotherapy to reduce acute and late toxicities.[40] Treatment volumes should at least include the tumor bed, initial extensions, and involved nodal areas. [41]

The role of prophylactic nodal irradiation remains debated, though recent studies suggest a significant benefit in advanced disease, with 5-year local control improving from 75% without to 98% with prophylactic irradiation. Most recurrences occur in levels Ib–III, supporting bilateral prophylactic coverage in Kadish C tumors. Recommended doses range from 60–70 Gy to the tumor site and 50–54 Gy to nodal areas at risk, achievable with modern IMRT despite the proximity of critical structures. [40]

CHEMOTHERAPY

Given its histological similarity to neuroblastoma, small-cell lung carcinoma, and other neuroectodermal tumors, esthesioneuroblastoma has been treated with chemotherapy regimens including cyclophosphamide, vincristine, doxorubicin, ifosfamide, and combinations of etoposide with cisplatin [42]. Chemotherapy has demonstrated greater efficacy in high-grade tumors (Hyams grade III–IV) compared with low-grade disease. In such high-grade cases, the preferred approach consists of complete surgical resection followed by adjuvant chemotherapy [42].

Neoadjuvant VIP chemotherapy (etoposide, ifosfamide, cisplatin) was reported by Kim et al. as effective in a series of 11 patients, with etoposide 75 mg/m², ifosfamide 1000 mg/m², and cisplatin 20 mg/m² administered on days 1–5 [43]. However, a literature review on sinonasal cancers by Bossi et al. concluded that chemotherapy can only be suggested, not formally recommended, due to limited evidence [44].

Nevertheless, a Mayo Clinic meta-analysis of 118 patients showed that multimodal treatment combining chemotherapy with surgery and/or radiotherapy significantly improved survival compared with monotherapy or no treatment ($p < 0.001$) [15].

Chemoradiotherapy

Esthesioneuroblastoma is both radiosensitive and chemosensitive, with reported response rates of 63–71%, supporting the role of combined chemoradiotherapy as primary treatment for locally advanced, unresectable cases [45], [46], [47]. A retrospective analysis from the University of Virginia involving 26 patients treated with neoadjuvant chemoradiotherapy showed a ≥50% tumor reduction in 16 patients (59%), a 20–50% reduction in 4 patients (15%), and no response in 6 patients (22%). Similarly, Dulguerov *et al.,* reported a 5-year overall survival rate of 51% following chemoradiotherapy [24].

A meta-analysis of studies published between 1990 and 2000, including 390 patients, reported an overall 5-year survival rate of 45% (SD ±22) and a disease-free survival of 41% (SD ±20). Survival outcomes differed according to treatment modality: 65% for surgery combined with radiotherapy, 51% for radiotherapy plus chemotherapy, 48% for surgery alone, 47% for trimodality therapy (surgery, radiotherapy, and chemotherapy), and 37% for radiotherapy alone.

In our series, survival analysis was limited by the small and non-representative sample size, with a mean overall survival of only 26 months.

The only universally recognized adverse prognostic factor in esthesioneuroblastoma is cervical lymph node involvement, and even more so distant metastases, most frequently pulmonary or osseous at diagnosis. Previous studies have demonstrated that nodal disease significantly reduces survival, without correlation between the primary tumor site and nodal involvement[48]. Positive surgical margins are also considered a negative prognostic factor by some

authors[27,48]. However, Chao et al. reported that margin status did not influence survival when surgery was followed by adjuvant radiotherapy[35].

Another hallmark of esthesioneuroblastoma is its high risk of late recurrence, sometimes decades after initial diagnosis, which mandates lifelong surveillance. Endoscopic examination and MRI remain the standard follow-up tools, with MRI considered the gold standard. PET-CT may provide additional information, though its sensitivity is limited by false positives in irradiated tissues. Surveillance should be intensive during the first years, then individualized, with lifelong follow-up strongly recommended in high-risk patients.

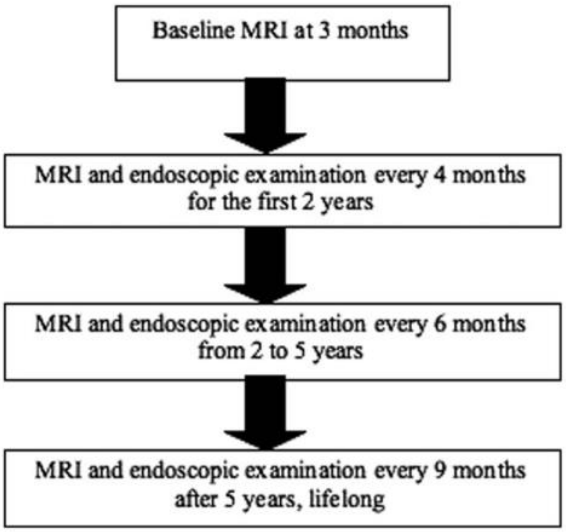

Figure 6 : Follow-up algorithm for esthesioneuroblastoma[3]

CONCLUSION

Esthesioneuroblastoma is a rare sinonasal malignancy with a high potential for recurrence, sometimes occurring decades after diagnosis, which mandates long-term surveillance. Complete surgical resection followed by adjuvant radiotherapy remains the standard approach for resectable tumors, while the role of endoscopic surgery, the optimal therapeutic sequence, and the contribution of chemotherapy—particularly in advanced stages—are still under debate. Management of cervical lymph nodes remains controversial in the prophylactic setting, although combined surgery and radiotherapy are required when nodal involvement is present. Given the rarity of this neoplasm and the limited size of reported series, treatment strategies remain heterogeneous. Establishing national or regional referral centers dedicated to esthesioneuroblastoma would allow centralized pathology and imaging review, specialized multidisciplinary tumor boards, and expert patient care. Increased awareness among healthcare professionals is also essential to achieve earlier diagnosis, which remains the key factor for improving prognosis.

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