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**Session:** Pediatric rare tumors

# **ESTHESIONEUROBLASTOMA IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS**

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## Abstract

The esthesioneuroblastoma (ENB) is characterized as a rare malignant sinonasal tumor of neuroectodermal origin. Its starting point is the olfactory epithelium located in the upper part of the nasal cavities. Different nomenclatures have been proposed, but the most common are “esthesioneuroblastoma” and “olfactory neuroblastoma.” ENBs have a bimodal distribution and mainly occur in teenagers, young adults and people aged 50-60. It is a very rare tumor in pediatrics since only around 100 cases have been reported so far. Within ENBs, we can distinguish tumors with different biological behavior ranging from localized forms with slow evolution to aggressive and metastatic forms at onset. In addition, precisely diagnosing undifferentiated tumors and distinguishing them from other etiologies of sinonasal tumors are sometime difficult. Added to its very low incidence, these characteristics make the study of ENB complicated. The standard treatment currently includes broad surgery followed by radiation therapy in localized resectable tumors. Neoadjuvant chemotherapy is indicated in large unresectable tumors and in metastatic forms. However, in certain indications, such as high-grade operable tumors, the role of perioperative chemotherapy remains to be defined. The objective of this analysis is to detail current knowledge regarding ENBs' epidemiological, biological, clinical and radiological characteristics as well as how to manage ENB in young patients.

**Keywords:** esthesioneuroblastoma, olfactory neuroblastoma, rare tumor, leptomeningeal relapse, radiotherapy, children

## Introduction

Berger et al. first described Esthesioneuroblastoma (ENB) in 1924 <sup>1</sup>. It was characterized as a rare malignant sinonasal tumor of neuroectodermal origin <sup>2</sup>. Its starting point is the olfactory epithelium located in the upper part of the nasal cavities. Different nomenclatures have been proposed, but the most common are “esthesioneuroblastoma” and “olfactory neuroblastoma.” It is a very rare tumor in pediatrics since only around 100 cases have been reported so far <sup>3-9</sup>. Within ENBs, can be distinguish tumors with different biological behavior ranging from localized forms with slow evolution to aggressive and metastatic forms at onset <sup>10</sup>.

The olfactory epithelium covers the upper section of the nasal cavities and presents specific regenerative abilities <sup>11</sup>. Olfactory mucous is found in the area of the cribriform plate of the ethmoid bone, the middle and upper sections of the turbinate bone and the upper

portion of the nasal septum. It is made up of different cellular types, including mature olfactory neuroepithelial cells, a basal layer of stem cells, subtentacular support cells and flat cells forming the Bowman glands in the olfactory *lamina propria* <sup>12</sup>. The olfactory epithelium is in contact with the cribriform plate of the ethmoid bone, which leads to close anatomical contact with the dura mater, the olfactory bulbs and the frontal lobe in the upper region, the nasal cavities and nasal septum in the lower region, the frontal sinus in the frontal region, the sphenoidal sinus and sella turcica towards the rear as well as with the ethmoidal cells and the maxillary sinus on both the right and left sides. These anatomical interactions may explain the growth tumors pattern.

## Epidemiology

ENBs represent between 3% and 6% of all sinonasal tumors in adults, while in children, these are dominated by rhabdomyosarcoma <sup>13</sup>. Incidences in adults are 0.4/million <sup>14</sup>. A bimodal distribution of the disease was described with 2 frequency peaks (2<sup>nd</sup> decade and 6<sup>th</sup> decade) <sup>15</sup>. However, a recent study of the SEER (*Surveillance, Epidemiology, and End Results*) database showed a unimodal distribution with a frequency peak during the 5<sup>th</sup> and 6<sup>th</sup> decades with a median age at diagnosis at 54 years old (1-91 years) <sup>16</sup>. In children, the median age at diagnosis is around adolescence. The development of an ENB at an early age is very rare. Nevertheless, cases were described in the neonatal period.

A slight male predominance in adults exists. No familial case of ENB has been reported in the literature and no genetic predisposition to cancer has been associated with ENBs. In addition, no environmental factors have currently been discovered <sup>17</sup>.

## Tumor biology

Several anatomical origins for ENB have been proposed: the vomeronasal organ, the sphenopalatine ganglion, the ectodermal olfactory placode, autonomic ganglions in the nasal

mucosa and the olfactory epithelium<sup>14,15</sup>. However, the basal progenitor cell of the olfactory mucosa is commonly accepted as ENB's originating cell site. Indeed, through progressive maturation, these basal cells will be differentiated into mature olfactory neurosensory cells from the basal membrane to the epithelium on the surface. The combination of neuronasal and olfactory specific markers makes it possible to distinguish these cells over the course of their maturation. The human homologue of the *ASCLI* gene (*Drosophila*) is expressed in immature olfactory neurons and is required for their development, while the *OMP* gene (*Olfactory Marker Protein*) is exclusively expressed in the mature olfactory neuron. It was demonstrated that *ASCLI* is expressed in ENBs unlike *OMP*, suggesting that this tumor results from an immature olfactory neuron of neuroectodermal origin<sup>18</sup>.

Several studies have focused on the somatic chromosomal alterations of ENBs. A characteristic profile of chromosomal reorganization was described with frequent deletions in the 1p, 3p/q, 9p and 10 p/q regions and amplifications in the 17q, 17p13, 20p et 22q regions. Tumors presenting relapses and metastases seem to have higher chromosomal instability than that of less aggressive tumors<sup>19</sup>. The 5, 6q, 7q, 11p/q, 15q21 deletions and the chromosomal gains in 1p32-p34, 1q12 and 2p22-p24 are, respectively, more frequently encountered in metastatic ENB lesions and are linked to a poorer prognostic. Some authors associate the amplification of the *MycN* oncogene (2p24 region) with the risk of progression<sup>20</sup>. An analysis of genomic alterations associated with ENB found potential genomic alterations that could be the target for treatment in more than half of the cases. The genes the most often concerned were *TP53*, *PIK3CA*, *NF1*, *CDKN2A* and *CDKN2C*<sup>21</sup>. The signal transductions for growth factors, mTOR and CDK could therefore represent therapeutic targets in this tumor.

## Clinical Presentation

The clinical manifestations upon diagnosis are non-specific and dependent on the local or regional tumoral extension <sup>22</sup>. ENB is a unifocal tumor and the symptoms are often unilateral <sup>17</sup>. They are dominated by rhinological manifestations with nasal obstruction associated with recurring epistaxis <sup>8,23</sup>. Headaches and hyposmia/anosmia may also be present <sup>24</sup>. These clinical signs can imitate the symptoms encountered in benign infections and therefore delay the diagnosis <sup>25</sup>. Classically, the delay between the appearance of clinical signs and the histological diagnosis is between 6 months and 1 year <sup>15</sup>. In extended forms, orbital extension can cause ophthalmological symptoms such as exophthalmia, diplopia and decreased visual acuity <sup>26,27</sup>. Extension to the anterior cerebral cavity can cause convulsive episodes. While these signs of intracranial or orbital extension are present in approximately 10% of adult patients, they are more frequent in children, affecting nearly half of cases <sup>8</sup>. A retrospective study of nasal cavity tumors in children showed that ophthalmological symptoms were the most frequent telltale clinical sign after nasal obstruction <sup>13</sup>. Paraneoplastic syndromes associated with ENB were described with, in particular, Cushing's syndrome confirmed through increased ACTH tumoral secretion with a return to normal values at the end of treatment, malignant hypercalcemia, hyponatremia due to inappropriate antidiuretic hormone secretion, and even an opsomyoclonus syndrome <sup>28-33</sup>.

## Diagnosis Methods

First and foremost, classically, an endoscopic exam of the nasal cavities makes it possible to visualize a peduncular, intranasal, unilateral mass with a smooth surface located in the area of the middle turbinate bone. The latter appears red and swollen due to rich vascularization. Sometimes, surface ulcerations and granulations can be present, specifically in high-grade tumors. Its size varies from that of a small node to that of a brittle voluminous

mass. Locally, an advanced illness can present signs of invasion and destruction of the neighboring structures such as the eye socket, brain, facial soft tissue and skin.

The initial radiological assessment most often includes a CT of the facial cavity and/or a cervical/cerebral MRI making it possible to evaluate the locoregional tumor's extent and establish a staging according to the Kadish classification <sup>15,23,34,35</sup> (Table I). On the CT-scan, all cases had an intranasal polypoidic lesion with an epicenter located on a unilateral olfactory recess responsible for an asymmetrical enlargement in the olfactory system and extending to the cribriform plate <sup>36</sup>. The cerebral MRI found a hypo/isointense tumoral aggregation in T1-weighted images and an iso/hyperintense mass in T2-weighted images with homogeneous and intense contrast enhancement after the injection of Gadolinium with the exception of the hemorrhagic and necrotic zones (Figure 1) <sup>37</sup>. This makes it possible to assess perineural dissemination, extension to the dura mater and subarachnoid space as well as intracranial extension <sup>17,38</sup>. Orbital extension is also closely evaluated on FAT-SAT sequence MRIs by either showing a clear boundary when there is no crossover to the orbital fascia or an irregular boundary, a sign of direct extension to the orbital cavity. MRIs often make it possible to distinguish between the tissular mass and a collection of non-tumoral secretions that appear distinct in T2 hyperintensity <sup>39</sup>. Studies report the presence of characteristic peritumoral and intracranial cysts in ENB <sup>40</sup>. While the Technetium bone scan, combined with an MRI if necessary, makes it possible to confirm the presence of bone metastases, specifically, in the area of the dorsal spine. On the CT, ENB appears like a homogeneous mass of soft tissue, with areas of necrosis and several calcifications that are especially present in cases of a voluminous tumor (Figure 2) <sup>41</sup>. The thin-slice CT with coronal and sagittal reconstructions sometimes enables a better evaluation of the bone extension than an MRI, specifically, in the area of the cribriform plate of the ethmoid bone, the papyraceous plate and the *fovea ethmoidalis* <sup>39</sup>. It often shows bone erosion in the orbital region and the base of the skull,

ranging from simple bone remodeling without destruction in slow-growth tumors to extensive bone destruction in cases of aggressive tumors <sup>17</sup>. The contrast uptake is homogenous and moderate. A chest-abdominal CT and/or hepatic ultrasound are indicated when searching for pulmonary and hepatic metastases <sup>39</sup>. Lymph node metastases are present in approximately 8-10% of adult patients at diagnosis <sup>17,42,43</sup>. Regional extension to the cervical lymph nodes must be evaluated clinically, via an MRI/cervical CT and a PET-FDG scan <sup>16</sup>. Indeed, the PET scan makes it possible to diagnose the presence of tumoral cervical adenopathies that are not detectable on a classic CT in nearly 20% of cases <sup>17,44,45</sup>. Furthermore, in addition to a conventional imaging assessment, the PET scan also makes it possible to evaluate distant metastatic extension, which has an impact on therapeutic care <sup>45</sup> (Figure 3).

Additionally, a radiological evaluation facilitates the differential diagnosis of other malignant tumors affecting the nasal cavities in adults, including epidermoid carcinoma, adenocarcinoma, sinonasal undifferentiated carcinoma, neuroendocrine carcinoma and non-carcinomatous tumors (sarcoma, lymphoma, melanoma) <sup>46,47</sup>. For some authors, a starting point in the region of the olfactory niche in the upper area of the nasal cavities and extension to the cribriform plate are very characteristic of an ENB diagnosis <sup>11</sup>. However, ectopic forms of ENB are possible involving the sphenoclivus or the maxillary sinus <sup>48,49</sup>. Moreover, malignant tumors (SNUC, Ewing sarcoma, or intestinal-type adenocarcinoma) or benign lesions (meningocele) may also develop in the olfactory niche region <sup>50</sup>.

Intra-tumoral calcifications and the presence of cysts in the region of the intracranial tumoral aggregation can orient the diagnosis <sup>40,51</sup>. A study evaluated the impact of a PET scan on the differential diagnosis between ENB and sinonasal undifferentiated carcinoma (SNUC). It showed that the uptake intensity of the primary SNUC tumor (measured with the SUV max value) was 5 times higher than that measured in ENBs <sup>52</sup>. In children, other sinonasal round

and blue small-cell tumors mainly include rhabdomyosarcoma, Ewing's sarcoma and the metastatic locations of neuroblastoma.

## Tumoral Staging

Optimal initial classification for ENBs remains a topic of discussion (Kadish or TNM staging). The purpose of all these classifications is to evaluate the risk of relapse/progression and guide locoregional treatment. Local extension can reach the paranasal sinuses, the skull base, the orbital bone, the cavernous sinus and the central nervous system (CNS). In total, 17% of adult patients present lymph node metastases upon diagnosis and 40% of all patients will develop lymph node extension during the disease's progression. ENB-based lymph node extension mainly affects cervical adenopathies in the regions II (90%), I and III (50%) and retropharyngeal adenopathies (40%). The regions IV and V are only affected in case of broad cervical metastatic dissemination<sup>17</sup>. Distant metastases can affect the lungs, liver, bones, bone marrow and meninges<sup>39</sup>.

The Kadish staging analyzes this extension based on tumoral diffusion from the nasal cavities towards adjacent anatomical structures (Table I). It was modified by Morita *et al.* with the addition of a stage D for patients presenting cervical or distant lymph node metastases<sup>53</sup>. In several studies, approximately 2/3 of patients presented Kadish C tumoral extension, illustrating the lack of discrimination among these patients within stage C, specifically regarding extension to the dura mater. The distinction between stages A and B occurs based on the extension to the paranasal sinuses, but these criteria do not modify the operable or non-operable character of the tumor<sup>17</sup>. Furthermore, stage A is very rarely represented due to the early extension to the ethmoidal sinus during tumoral development (less than 5% of cases)<sup>39</sup>. A recent study evaluated the prognostic meaning of the Kadish staging for ENB by using American data from the *National Cancer Database*. In this study, there was no correlation between survival and the Kadish grades for the early stages<sup>54</sup>. For

children, the clinical presentation is very often locally more advanced than in adults with a majority of tumors categorized as Kadish stage C and D and therefore, not operable in first-line treatment. This classification, however, was recently confirmed to be statistically correlated with the pediatric prognostic <sup>9</sup>.

In adults, this classification has the tendency to be supplanted by the Dulguerov TNM classification, which makes it possible to better evaluate regional and distant extension. One of the major relapse risk factors is the presence of cervical adenopathies responsible for an unfavorable prognostic (Table II) <sup>15,55</sup>. Consequently, this classification makes it possible to differentiate between the diseases with poor prognoses and identify the patients with a very high risk of locoregional relapse <sup>17</sup>. Furthermore, the Dulguerov classification takes into account the early invasion of the cribriform plate of the ethmoid bone as of the T2 stage and separates intracranial and extradural extension from the characteristic invasion of the frontal lobe <sup>39</sup>. Arnold *et al.* recently published a meta-analysis comparing Kadish and modified Dulguerov staging systems showing that both systems correlated with disease-free survival and overall survival, with superior performance in the Dulguerov system <sup>56</sup>.

## Histological Characteristics

The histological diagnosis for ENB is often difficult and systematically requires confirmation by a pathologist within a network of experts in pediatric and ENT pathology. Histologically-speaking, the presence of a population of round small cells, within a fibrillated intercellular stroma, associated with Homer-Wright rosettes strongly indicates ENB if the tumor's origin is located in the upper section of the nasal cavities. ENB belongs to the "round and blue small-cell tumor" family of the nasal cavities and paranasal sinuses. It is characterized by morphological heterogeneity according to the degree of differentiation. The Hyams grading evaluates the aggressiveness of the primary tumor. It describes 4 stages of

differentiation according to histological criteria like glandular differentiation, the presence of mitosis or necrosis. It reflects ENB biology, ranging from indolent forms to aggressive and metastatic forms (grade I (differentiated) to grade IV (undifferentiated)) (Table III) <sup>57,58</sup>. Low-grade lesions (Hyams I and II) present a recognizable histological aspect characterized by lobular architecture composed of primary neuroblastic cells. The tumoral cells are small and round with a strong nuclear-cytoplasmic relationship. The nuclei are small and uniform with thin chromatin and rare nucleoli <sup>42</sup>. Cell clusters are separated by a richly vascularized fibrous stroma. Nuclear pleomorphism is variable and often low. Mitoses and necrotic zones are rarely represented. The Flexner-Wintersteiner rosettes and the Homer-Wright pseudo-rosettes are present in 30% of cases with a characteristic neurofibrillary stroma. Calcifications may be present. Inversely, high-grade undifferentiated lesions (Hyams III and IV) present significant nuclear pleomorphism with considerable mitotic activity and broad necrotic zones. The architecture is diffuse and loses its glandular character. In this case, the differential diagnosis is raised with the other undifferentiated sinonasal-localized tumors. In immunohistochemistry, ENB presents a diffuse positivity of NSE (*Neuron-Specific Enolase*), synaptophysin and chromogranin, specific markers of neuroendocrine differentiation. Variable positivity is observed for cytokeratins, vimentin, EMA (*Epithelial Membrane Antigen*) and CD56 <sup>20</sup>. PS-100 positivity is visible on the periphery of the tumor in the region of subtentacular cells. ENB tests negative for desmin, myogenin and actin. The Ki-67 proliferation index is high, between 10-50% <sup>59</sup>.

The Hyams grading is nevertheless subjective and the separation between the 4 stages is sometimes difficult. Some authors have grouped together low-grade tumors (Hyams I and II) and high-grade tumors (Hyams III and IV) in order to better correlate the grade upon prognostic <sup>60</sup>. Grade III/IV tumors are associated with more significant locoregional extension and poor survival compared to low-grade tumors <sup>11,61</sup>. The high Hyams grade also correlates

with the presence of cervical adenopathies, locally advanced forms and non-operable diseases upon diagnosis <sup>17</sup>. However, in addition to its subjectivity, the Hyams grading is sometimes criticized because the discriminating value of each histological criterion is not well defined. Furthermore, molecular analyses of ENB have not reported obvious differences between low-grade and high-grade tumors, which could explain the difference in biological behavior between the 2 groups <sup>19</sup>. However, it should be noted that a recent retrospective national study on ENB in children and adolescents showed that this histological classification appeared as a prognostic for this population <sup>9</sup>.

## Differential Diagnoses

The ENB diagnosis is especially difficult for high-grade undifferentiated tumors and its differential diagnoses are many <sup>37</sup>. No pathognomonic molecular marker exists to help with the diagnosis. In children, in this sinonasal location, the differential diagnoses for ENB are mainly: rhabdomyosarcoma, diffuse large B-cell lymphoma cells, non-rhabdomyosarcoma soft tissue sarcomas and Ewing's sarcoma. ENB tests negative for CD99 and FLI-1, which makes it possible to differentiate it from primary neuroectodermal tumors (PNET)/Ewing's sarcoma. A positivity of muscular differentiation markers (desmin, myogenin, vimentin, actin) will lead to a rhabdomyosarcoma diagnosis. In case of doubt, the absence of specific translocations in pediatric sarcomas (alveolar rhabdomyosarcoma, synovial sarcoma, Ewing's sarcoma, etc.) can help with the diagnosis. From the description of SNUC, a differential diagnosis with high-grade ENB is complicated. Compared to SNUC, ENB is a lower grade tumor with neuroectodermal differentiation. SNUC presents extensive necrotic areas and hemorrhagic zones making it possible to orient the diagnosis. The presence of focal neuroendocrine differentiation within SNUC should raise the question regarding an ENB diagnosis. In immunohistochemistry, ENB tests positive for NSE and pS-100 unlike

neuroendocrine carcinoma and SNUC <sup>17</sup>. Reactivity to cytokeratins can be discriminating in the differential diagnosis of SNUC and small-cell neuroendocrine carcinoma. Recently, loss of *SMARCB1* expression has been reported in a small number of sinonasal carcinoma which harbor an aggressive behavior with a poor prognosis <sup>62,63</sup>. As for undifferentiated carcinoma of the nasopharynx (UCNT), it presents squamous differentiation and a relationship with the Epstein-Barr virus (EBV) easily analyzable in immunohistochemistry (EBER, LMP) <sup>19,64</sup>. Giant pituitary adenoma is rarely found in this location, since it originates from the extension of an intrasellar or ectopic tumor <sup>37</sup>. ENB can be distinguished from the rare form of sinonasal mucous melanoma through its pS-100 positivity topography, which affects tumoral periphery in the region of the subtentacular cells in ENB.

## Treatments

A multimodal treatment combining chemotherapy, surgery and radiotherapy is currently proposed and seems to show favorable results highlighting the importance of this type of treatment and this tumor's sensitivity to chemotherapy <sup>6,9,65</sup>. The treatment of reference in adults remains surgery followed by radiotherapy. However, in more advanced forms, chemotherapy before or after surgery can play a role that still remains to be defined <sup>9,65,66</sup>.

## Surgery

The historical surgical approach in the treatment of ENB was an anterior cranial-facial resection via the paralateral nasal channel. This method enables good visualization of the tumor and its extension, an en bloc resection of the mass and reconstruction facilitated by a vascularized pericranial flap <sup>67</sup>. However, endoscopic approaches have been developed and becomes the standard of care for ENB surgery enabling a good local control and a decrease in

post-surgical morbidity compared to cranial-facial resection surgery<sup>9,68-71</sup>. Moreover, endoscopic endonasal approach (EEA) is now used in the treatment of more advanced tumors allowing for a good rate of complete resections without the morbidity related to the necessity of a facial incision or retraction of the frontal lobe in case of a craniotomy<sup>72,73</sup>. An endonasal endoscopy gives access to the base of the skull and the papyraceous plates and enables the excision of the dura mater, the olfactory tract and bulbs as well as the cerebral parenchyma. Recently, the development of expanded EEA, alone or in combination with craniotomy, enable surgical resection of most cases of ENB<sup>68,71,72,74</sup>.

Closing off communication between the nasal cavities and the anterior cerebral fossa is primordial in order to prevent cerebrospinal fluid from leaking and causing an ascending meningitis. It was reported that the rate of complications especially cerebrospinal fluid leakage after EEA is less frequent than after a cranial-facial resection<sup>71,74,75</sup>. The reduction in postoperative morbidity after EEA allows the adjuvant treatment to be carried out in the shortest possible time. It might help to avoid the early relapses described in pediatric cases<sup>9</sup>. Neuronavigation may be a promising technique in order to improve surgical treatment<sup>76</sup>. Positivity in the resection margins is a major unfavorable prognostic factor for ENB<sup>72,77</sup>. The role of neoadjuvant treatment remains in question, but could easily make it possible to obtain a resection that is microscopically more complete by decreasing tumoral volume.

No publication has studied the difference between the surgical techniques in terms of survival and morbidity in pediatric-aged patients. More significant tumoral spread in children could make the use of endoscopic techniques difficult. Pediatric anatomical specificities (facial size, development, etc.) are factors influencing surgical techniques in children. The main post-surgical complications for this type of tumoral resection are infectious meningitis, chronic sinus issues and anosmia/hyposmia during the resection of the olfactory bulbs<sup>9</sup>.

## [Radiotherapy](#)

The higher frequency of local or locoregional relapses of ENB in cases of exclusive surgical treatment encourages us to propose complementary treatment via radiotherapy. This adjuvant treatment is classically indicated in cases of incomplete resections, macroscopic residue, relapse and in cases of high-grade or locally advanced tumors <sup>37</sup>. For some authors, the only indication for surgery without complementary radiotherapy would be Kadish A stage tumors with clean resection margins <sup>17</sup>. In adults, the average administered dose proposed is around 60 Gy (55-65 Gy) in 30 to 33 fractions <sup>16</sup>. Post-radiation complications decreased with current techniques like intensity-modulation radiotherapy therapy (IMRT) and tomotherapy. Proton therapy showed good results for long-term survival with less radiation-induced toxicity <sup>78,79</sup>. A study showed the efficacy of radiotherapy (50 Gy) combined with concurrent chemotherapy in the neoadjuvant treatment of widely extended ENB, not operable upon diagnosis <sup>80</sup>. In pediatrics, the contribution of proton therapy in at-risk tumoral localization treatment, such as ENB, could make it possible to also limit secondary effects by saving healthy peritumoral soft tissue. The main complications expected after radiotherapy are endocrinological and ophthalmological damage (cataract, keratitis, retinal fibrosis, retinopathy). Local irradiation can, however, worsen sinus issues following surgery.

### Chemotherapy

Indications for chemotherapy concern high-grade lesions, positive or borderline resection margins, cases of tumoral relapse, non-operable tumors and regional or distant metastatic forms. Up until now, no protocol has compared through comparative prospective studies the best medicinal strategy for this tumor, even if platinum-based chemotherapy is mainly used in adults <sup>17,37</sup>. However, some teams use treatment protocols using cyclophosphamide, vincristine and doxorubicin <sup>81</sup>. As for high-grade ENBs, some authors justify the usage of a multimodal treatment including chemotherapy, by comparing the evolution and aggressiveness of these tumors with SNUCs and small-cell neuroendocrine

carcinomas <sup>56</sup>. A study showed a response rate to neoadjuvant chemotherapy (cisplatin-etoposide) of nearly 70% <sup>66</sup>. Even if the role and type of chemotherapy remains to be defined, its usage in addition to surgery and radiotherapy seems to benefit patients' survival. De Bonnecaze *et al.* showed that stage C tumors were mainly treated with surgery followed by radiotherapy (36%) while stage D tumors were more frequently treated with concurrent radio-chemotherapy (48%). Overall survival at 10 years found better results for the combination of surgery-radiotherapy-chemotherapy than surgery-radiotherapy, 60% vs. 46%, respectively. Chemotherapy, therefore, seemed to decrease the risk of relapse over the very long term <sup>76</sup>.

### Treatment of Cervical Lymph Nodes

In case of cervical metastases, conventional treatment includes lymph node curettage combined with cervical irradiation <sup>82</sup>. However, the treatment of lymph nodes in patients without cervical metastases upon diagnosis remains in question. Some authors showed that prophylactic lymph node irradiation in adults reduces the risk of cervical relapse, but without any beneficial effect on survival <sup>83</sup>. For others, prophylactic radiotherapy does not prevent these lymph node relapses <sup>84</sup>. In pediatrics, a recent study showed that cervical lymph node evolution is uncommon in this population leading us to believe that prophylactic cervical irradiation does not seem necessary here <sup>9</sup>.

### Prognostic and Evolution

Many authors have attempted to characterize the prognostic factors influencing the evolution of ENBs. However, due to the rarity of the disease, the results are sometimes contradictory or do not reach the threshold of significance. Tumoral extension upon diagnosis is a significant prognostic factor. Higher Kadish stages, lymph node extension and distant metastases are markedly associated with an unfavorable prognostic <sup>9,16,85</sup>. In another study, orbital and/or intracranial extension represented a factor for a poor prognostic with 55.6% overall survival at 5 years for patients with orbital extension compared to 88.3% for patients

without orbital or intracranial extension and 41.7% for patients presenting intracranial extension <sup>86</sup>. For most authors, high-grade tumors have a higher risk of leptomeningeal metastasis and low-grade tumors have a greater risk of local relapse <sup>19</sup>. The higher Hyams grades are therefore markedly associated with an unfavorable prognosis, specifically for grade IV tumors <sup>9,16,85</sup>. From a pathological point of view, the mitotic index and the presence of necrosis are considered as pejorative factors. Inversely, tumors presenting S-100 positivity and a low Ki67 proliferation index have better tumoral differentiation and, thus, a better prognosis <sup>19,60</sup>. The tumoral and progressive characteristics of the principal pediatric cohorts published thus far are indicated in Table IV.

Long-term monitoring is important because delayed local relapses of esthesioneuroblastoma have been described 10 years after the end of treatment <sup>87</sup>. Long-term monitoring requires, besides a clinical exam, regular cerebral and cervical MRIs supplemented with a chest x-ray. The PET scan enables the early detection of local and metastatic relapses, but its repetition poses questions for children <sup>17</sup>.

## Conclusions

ENB is a rare and heterogeneous tumor with variable prognostics. The differential diagnosis for undifferentiated tumors is difficult. Cranial-facial resection surgery plays an important role in extended tumors, but endoscopic techniques enable good local control by decreasing morbidity. The indications for chemotherapy and systematic cervical irradiation are still being discussed. Tumoral extension (Kadish C-D) and the histological grade (Hyams III-IV) represent an unfavorable prognosis and motivate an extremist approach. To summarize, we proposed a diagnostic work-up and therapeutic options in Figure 4, based on the literature review and authors' opinion. Molecularly characterizing ENB would make it possible to understand its tumorigenesis and the biological heterogeneity between low-grade

and high-grade tumors. The discovery of genomic alterations would open new therapeutic perspectives by targeting certain signal transductions or reactivating the immune response through immune checkpoint inhibitors. In case of relapsing or resistant ENBs, the molecular characterization of the tumor's genomic alterations could help identify potential therapeutic targets. Wang *et al.* reported the case of a patient with relapsed ENB treated with a combination of Cetuximab, an EGF (*Epidermal Growth Factor*) pathway inhibitor and Sunitinib, a tyrosine kinase inhibitor (PDGFR, FLT3, RET, etc.), who is in complete remission after 1 month of treatment. The therapeutic choice was guided by WES (*Whole Exome Sequencing*) sequencing, which found somatic mutations in the region of the *EGFR*, *FGFR2*, *KDR* and *RET* genes <sup>88</sup>. A recent ENB study showed a phosphorylation level of 90% for pERK, 50% for pAKT and 70% for pSTAT3 in immunohistochemistry. Recently, Classe *et al.* reported an integrative multiomics analysis of ENB identifying two subgroups of ENBs: neural-like and basal-like <sup>89</sup>. They showed that the basal-like subgroup includes poorly differentiated tumors with a high expression of embryonic genes and the shorter survival of patients sharing some similarities with our cohort of pediatric ENBs. Interestingly, basal-like ENBs harbor IDH2 mutations in one-third of cases, which might represent a therapeutic option <sup>89</sup>.

The authors declare that they do not have any conflict of interest with the information discussed in this article.

## Figure legends

**Figure 1.** MRI aspect of an esthesioneuroblastoma infiltrating the entire nasal cavity and extending into the left maxillary sinus in a 13-year-old adolescent female.

**Figure 2.** CT of the facial bones of a young 13-year-old girl diagnosed with an esthesioneuroblastoma infiltrating the right maxillary sinus with significant calcifications.

**Figure 3.** Full-body PET-FDG scan of a young 14-year-old girl presenting an extended esthesioneuroblastoma of the facial bones with lymph node and osteomedullar extension. Full-body MIP (A), axial fusion image (B) and CT (C).

**Figure 4.** Proposal for patients care with esthesioneuroblastoma.

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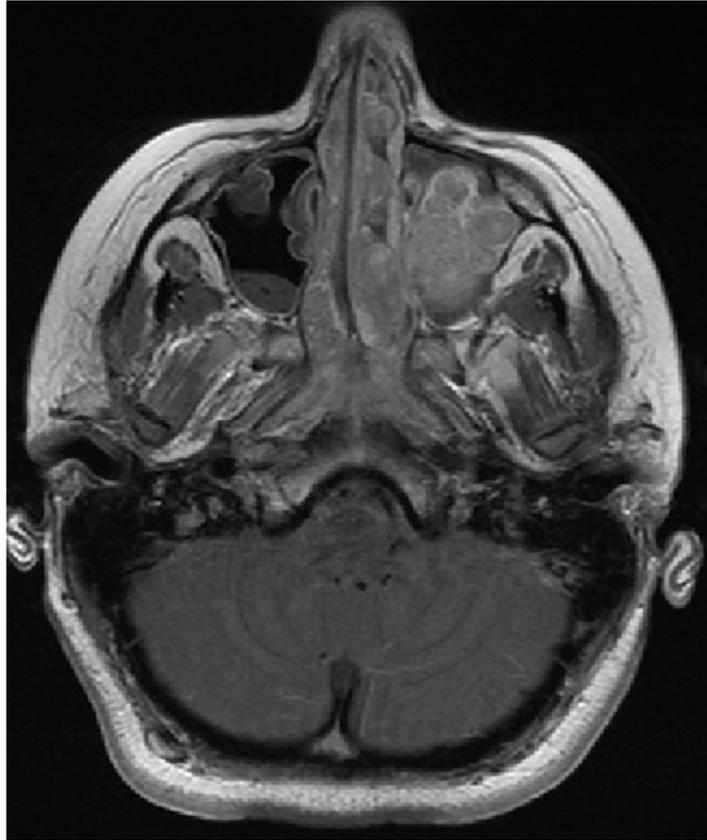
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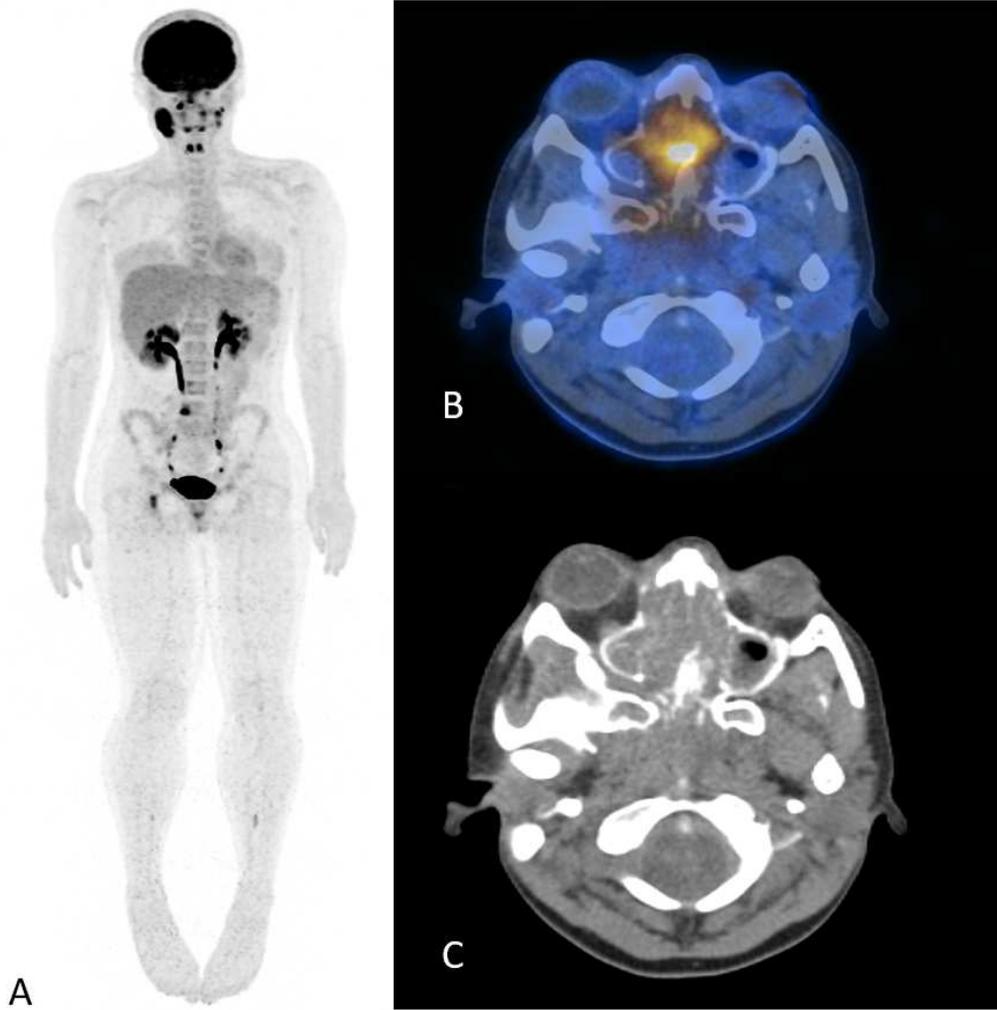
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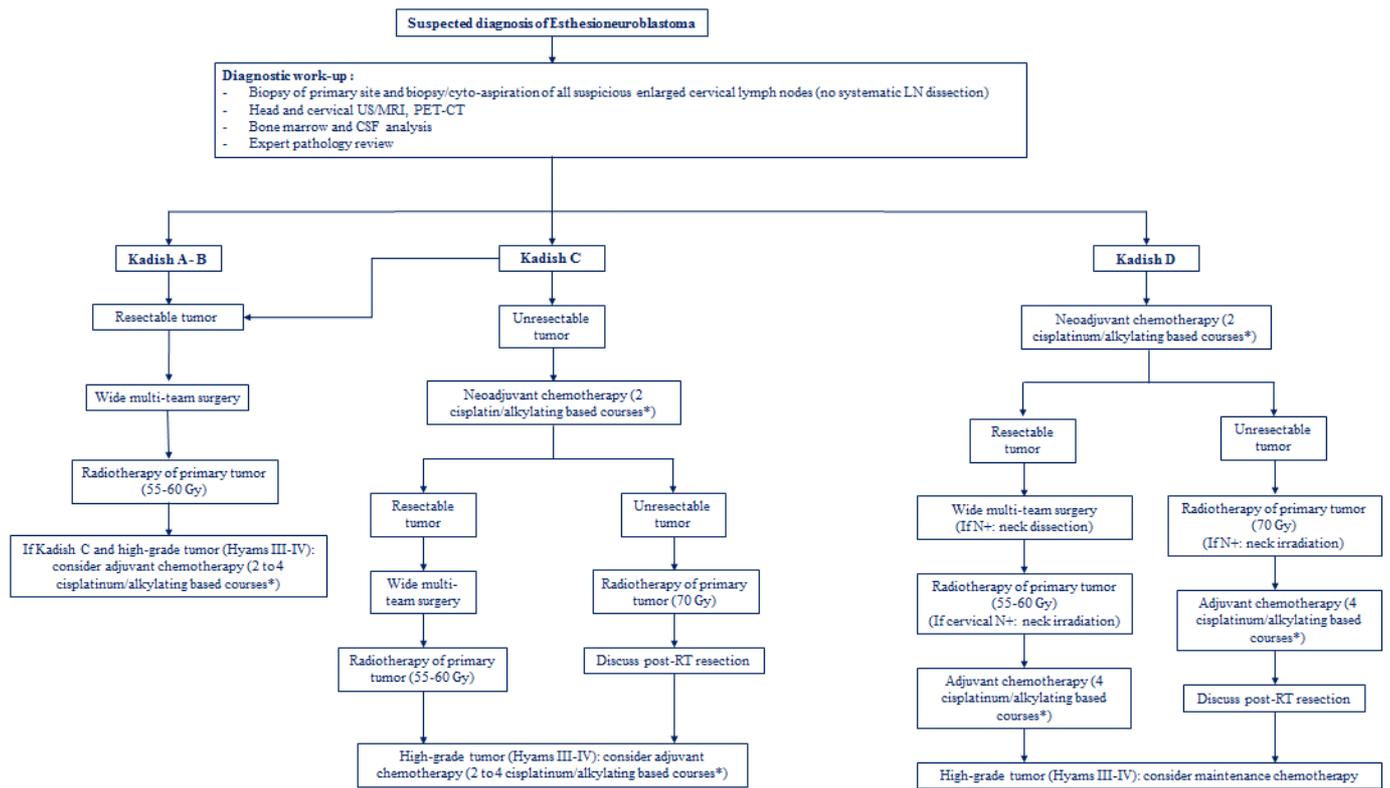
**Figure 1.** MRI aspect of an esthesioneuroblastoma infiltrating the entire nasal cavity and extending into the left maxillary sinus in a 13-year-old adolescent female.



**Figure 2.** CT of the facial bones of a young 13-year-old girl diagnosed with an esthesioneuroblastoma infiltrating the right maxillary sinus with significant calcifications.



**Figure 3:** Full-body PET-FDG scan of a young 14-year-old girl presenting an extended esthesioneuroblastoma of the facial bones with lymph node and osteomedullar extension. Full-body MIP (A), Axial fusion image (B) and CT (C).



\*Platinum-based regimen with etoposide-cisplatinum or etoposide-carboplatin/ alkylating-based regimen with ifosfamide-vincristine-actinomycinD-doxorubicin

**Figure 4.** Proposal for patients care with esthesioneuroblastoma

<b>Stage</b>	<b>Tumoral extension</b>
<b>A</b>	Tumor confined to the nasal cavities
<b>B</b>	Tumor extended to the nasal cavities and paranasal sinuses
<b>C</b>	Tumor extended past the nasal cavities and paranasal sinuses
<b>D</b>	Presence of metastases (regional or distant)

**Table I.** Modified Kadish staging

<b>Stage</b>	<b>Tumoral extension</b>
<b>T1</b>	Tumor invading the nasal cavity and/or the paranasal sinuses, but sparing the sphenoidal sinus and upper ethmoidal cells
<b>T2</b>	Tumor invading the sphenoidal sinus and/or the cribriform plate
<b>T3</b>	Tumor extended to the eye socket or the anterior cerebral fossa, without invasion of the dura mater
<b>T4</b>	Tumor invading the cerebral parenchyma
<b>N0</b>	Absence of regional lymph node metastases
<b>N1</b>	Presence of regional lymph node metastases
<b>M0</b>	Absence of distant metastases
<b>M1</b>	Presence of distant metastases

**Table II.** TNM classification of esthesioneuroblastoma according to Dulguerov.

<b>Grade</b>	<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>
<b>Architecture</b>	Lobular	Lobular	Variable	Variable
<b>Mitotic activity</b>	Absent	Present	Significant	Major
<b>Nuclear pleomorphism</b>	Absent	Moderate	Significant	Major
<b>Fibrillated matrix</b>	Prominent	Present	Minimal	Absent
<b>Rosettes</b>	Homer-Wright	Homer-Wright	Flexner-Wintersteiner	Flexner-Wintersteiner
<b>Necrosis</b>	Absent	Absent	Present	Customary

**Tableau III.** Hyams histological grading.

**Table IV.** Principal recent published pediatric cohorts

Reference [Publication year]	Number of patients	Median age (range)	Sex	Kadish grade	Median follow-up (range)	Outcome
Venkatramani R <sup>3</sup> [2016]	24	14 years (0.6 – 20)	F = 18 M = 6	B = 8 C = 8 D = 8	NA	5 years EFS 73.7% (50.5 – 87.3%) 5 years OS 72.8% (46 – 87.9%)
Lucas JT <sup>5</sup> [2015]	8	10 years (4 – 21)	F = 6 M = 2	B = 3 C = 1 D = 4	4.6 years (0.8 – 9.4)	5 years OS 87.5 %
Kababri ME <sup>4</sup> [2014]	11	14 years (0.8 – 18)	F = 8 M = 3	B = 5 C = 6	8.8 years (3.8 – 16.4)	5 years EFS 91% (62 – 98%) 5 years OS 91% (62 – 98%)
Bisogno G <sup>6</sup> [2012]	9	9.9 years (0.9 – 18)	F = 3 M = 6	B = 3 C = 6	13.4 years (9.2 – 22.9)	5 years EFS 77.8% (36.6% – 93.9%) 5 years OS 88.9% (43.3 – 98.4%)
Eich HT <sup>8</sup> [2005]	19	14 years (5 – 20)	F = 10 M = 9	B = 4 C = 15	3.1 years (0.3 – 23)	5 years EFS 55% (±13%) 5 years OS 73% (±12%)
Kumar M <sup>7</sup> [2002]	5	13 years (5 – 16)	F = 1 M = 4	A = 1 B = 1 C = 3	NA	NA
Dumont B <sup>9</sup> [2020]	18	12.2 years (0.9 – 18)	F = 8 M = 10	A = 1 B = 3 C = 10 D = 4	2.4 years (0.3 – 17.9)	5 years EFS 44.4% (±11.7%) 5 years OS 44.4% (±11.7%)

**Abbreviations:** OS, overall survival; EFS, event-free survival; NA, non-applicable.