Received: 30 July 2019 | Revised: 12 December 2019 | Accepted: 14 December 2019

DOI: 10.1002/pbc.28154

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

# Pattern of loco-regional relapses and treatment in pediatric esthesioneuroblastoma: The French very rare tumors group (*Fracture*) contribution

**Benoît Dumont**[1] | **Brice Fresneau**[2] | **Line Claude**[3] | **Anne-Sophie Defachelles**[4] | **Vincent Couloigner**[5] | **Stéphanie Puget**[6] | **Hervé J Brisse**[7] | **Paul Fréneaux**[8] | **Brigitte Lacour**[9,10] | **Daniel Orbach**[1]

[1]SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, PSL University, Paris, France

[2]Department of Pediatric and Adolescent Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France

[3]Department of Radiation Oncology, Léon Bérard Center, Lyon, France

[4]Department of Pediatric Oncology, Oscar Lambret Center, Lille, France

[5]Pediatric Head and Neck Surgery and Otorhinolaryngology Department, Necker Enfants-Malades Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France

[6]Pediatric Neurosurgery Department, Necker Enfants-Malades Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France

[7]Imaging Department, Institut Curie, Paris, France

[8]Department of Biopathology, Institut Curie, Paris, France

[9]National Registry of Childhood Solid Tumors, CHU de Nancy, Vandœuvre-lès-Nancy, France

[10]Inserm U1153, Center of Research in Epidemiology and Statistics (CRESS), Paris University, Epidemiology of Childhood and Adolescent Cancers Team (EPICEA), Paris, France

**Correspondence**
Benoît Dumont, SIREDO Oncology Center (Care, Innovation and Research for Children, Adolescents and Young Adults with Cancer), Institut Curie, PSL University, 26, Rue d'Ulm, 75248 Paris Cedex 05, France.
Email: benoit.dumont@curie.fr

## Abstract

**Background:** Esthesioneuroblastoma (ENB) is a rare neuroectodermal tumor that seldom occurs during childhood. Multimodal treatments are currently proposed, but the place of each therapy is still in debate. Our objective is to describe clinical evolution, especially the pattern of relapses and determine contributors to tumor progression.

**Procedure:** Medical charts of all children (≤18 years) affected by ENB treated in France from January 1990 to December 2015 were retrospectively analyzed.

**Results:** Eighteen patients were selected (10 males). Median age at diagnosis was 12.2 years (0.9-18). Tumor extension was Kadish stage A (n = 1), B (n = 3), C (n = 10), and D (n = 4). Hyams histological grades were I (n = 1), II (n = 3), III (n = 6), and IV (n = 6) (in two cases not defined). Initial cervical nodal spread was assessed by magnetic resonance imaging (n = 15), computed tomography scan (n = 16), fluorodeoxyglucose-positron emission tomography-computed tomography (n = 7), and cytological/histological analysis (n = 2). N1 stage was confirmed by imaging in two of 18 cases and one of two cases had cervical node dissection with neck irradiation (58 Gy). After a median follow-up of survivors of 7.6 years (3.8-17.9), 10 patients developed neuromeningeal progression, whereas no cervical nodal relapse occurred and only eight survived. Both 5-year overall and event-free survival rates were 44.4% (±11.7%).

Abbreviations: CFR, craniofacial resection; CNS, central nervous system; CPNI, cervical prophylactic nodal irradiation; CR, complete remission; CT, computed tomography; EER, endoscopic endonasal resection; EFS, event-free survival; ENB, esthesioneuroblastoma; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography-computed tomography; RT, radiation therapy; SFCE, Société Française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent; SUV, standardized uptake value.

**Conclusions:** The poor prognosis is mainly related to neuromeningeal dissemination that should be considered during treatment strategy. However, cervical lymph node relapse is rare.

**KEYWORDS**
children, esthesioneuroblastoma, leptomeningeal relapse, olfactory neuroblastoma, radiotherapy, rare tumor

## 1 | INTRODUCTION

Esthesioneuroblastoma (ENB) or olfactory neuroblastoma (ICD-O M9522/3) is a neuroectodermal tumor originating from neural crests. It derives from the olfactory neuroepithelium of the nasal vault. This malignant tumor remains exceptional during childhood with less than 100 cases reported up to now.[1–6] It mainly occurs during adolescence (median age: 9.9-14 years). In adulthood, ENB represents 3-6 % of all sinonasal tumors, whereas this site in children is dominated by rhabdomyosarcoma.[7] At diagnosis, clinical signs are nonspecific with nasal obstruction, rhinorrhea, or epistaxis.[5] Physical signs depend on tumor location and its extent. Initial presentation may mimic benign infections and delay the diagnosis. A magnetic resonance imaging followed by an endoscopic investigation is useful, allowing local disease staging and tumor biopsy. A pathological Hyams grading system uses histological criteria such as glandular differentiation, the presence of mitosis and necrosis to evaluate tumor differentiation.[8] Initial presentation in children differs from adults often because of large tumor extension often involving the eye socket and causing ophthalmological signs, which is the second most frequent sign after nasal obstruction.[7] Local extension may concern paranasal sinuses, the eye sockets and the skull base with involvement of the cavernous sinus, and eventually the central nervous system (CNS) with the risk of leptomeningeal involvement. Metastatic extension may involve cervical adenopathy and other distant organs (bone, liver, and lung). Tumor staging is usually described with the Kadish system.[9,10] However, this remains controversial and other staging systems have emerged, such as the TNM staging system.[11]

The current treatment strategy in adults includes surgery followed by radiation therapy.[12–16] Chemotherapy might be used in case of high-grade, recurrent, or locoregionally advanced tumors.[17–19] In pediatric cases, chemotherapy combined with surgery and radiotherapy (RT) is often the treatment of choice in advanced diseases compared to adult ones.[3,6] The incidence of cervical node metastases is about 10% at diagnosis but can increase to 20% during the disease in adults.[20–22] Local control with surgery and radiotherapy is a cornerstone of the treatment to avoid local and regional relapse. CNS relapse is described in pediatric ENB.[1,4] CNS and leptomeningeal involvement harbor a very bad prognosis. However, radiation therapy indications have to be discussed because of the late effects in the specific pediatric population.

Our objective is to retrospectively describe the initial presentation and outcome of a pediatric patient cohort affected by ENB and treated with a multimodal strategy in order to describe the pattern of loco-regional relapse in relation with treatments. Secondary objectives are to identify contributors associated with relapse type and survival rates in children, the benefit of cervical prophylactic nodal irradiation (CPNI), and discuss the current treatment strategy through comparisons with adult recommendations.

## 2 | METHODS

This retrospective national study selected all French patients from 0 to 18 years of age with a diagnosis of ENB or olfactory neuroblastoma (ICD-O M9522/3) confirmed by expert pathologists and treated from January 1990 to December 2015. Cases were extracted from the French *Registre National des Tumeurs Solides de l'Enfant*, the rare pediatric tumor study group database (*Fracture*),[23] and by directly questioning clinicians and pathologists at the *Société Française de lutte contre les Cancers et les leucémies de l'Enfant* (SFCE). This study complied with the reference methodology MR-004 from the *Commission Nationale de l'Informatique et des Libertés* (CNIL). Institutional review board approval was obtained for the study.

The clinical presentation, radiological pattern and histological characteristics, treatment, evolution, and complications were directly extracted from the medical file. Diagnostic imaging classified the primary tumor according to modified Kadish criteria: stage A, tumor limited to the nasal cavity; stage B, tumor infiltrating the paranasal cavities; stage C, tumor extended beyond the paranasal cavities infiltrating the orbital cavity, skull base, or CNS; stage D, regional extension (cervical adenopathy) or distant sites.[9,10] "Locoregional dissemination" referred to the involvement of the sinonasal tract directly in contact with primary tumor, the cervical lymph node, the anterior cranial fossa, and the leptomeningeal compartment due to the proximity of the tumor's origin site and the dura mater.

The lesion was histologically graded in accordance with the Hyams classification when the histological report mentioned it but no specific pathological review was done.[8] In addition, we compared two distinct risk groups of ENB: low grade (Hyams I and II) and high grade (Hyams III and IV). Patients with lumbar puncture at diagnosis were recorded.

The response to induction chemotherapy was evaluated after two to three courses according to the RECIST (Response Evaluation Criteria In Solid Tumors) 1.1 criteria.[24] Treatment-related sequelae were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (v4.03).

**TABLE 1** Clinical characteristics and outcome of the patients with ENB

| Patient | Age (year) | Sex | Kadish (metastatic sites) | Dulguerov TNM staging | Neoadjuvant chemotherapy | Tumor response | Adjuvant chemotherapy | Surgery | Neck dissection | Radiotherapy on primary (Gy) | Cervical radiotherapy (Gy) | Outcome | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 13 | M | A | T1N0M0 | No | - | No | Endonasal endoscopic resection | No | 56 | No | Alive without disease/recurrence | 74 |
| 2 | 13 | F | B | T2N0M0 | 2 CADO | SD | No | Multidisciplinary cranio-facial resection | No | 54 | No | Alive without disease/recurrence | 185 |
| 3 | 13 | F | B | T1N0M0 | 2 VP16-carboplatin | PR | No | Endonasal endoscopic resection | No | 56 | No | Alive without disease/recurrence | 86 |
| 4 | 13 | F | B | T2N0M0 | No | - | No | Cranio-facial resection | No | 54 | No | Alive without disease/recurrence | 55 |
| 5 | 13 | F | C | T3N0M0 | 2 VP16-cisplatin/ 2 CADO | PR | 1 VP16-carboplatin | Cranio-facial resection | No | 56 | No | Alive without disease/recurrence | 208 |
| 6 | 16 | M | C | T4N0M0 | 2 Oral VP16/ 1 oral EDX | PD | No | No | No | No | No | DOD | 4 |
| 7 | 7 | M | C | T3N0M0 | 6 VIDE/1 VAI | PR | 7 VAI | No | No | 54 | No | Alive without disease/recurrence | 46 |
| 8 | 18 | M | C | T4N0M0 | 4 CADO | PR | No | Multidisciplinary cranio-facial resection | No | No | No | DOT | 8 |
| 9 | 8 | F | C | T3N0M0 | 2 CADO | PR | No | Endonasal endoscopic resection | No | No | No | DOD | 41 |
| 10 | 10 | M | C | T4N0M0 | 1 IE/1 IFO-Actino/ 2 EDX-Adria | SD | 2 IE/2 EDX-Adria | Multidisciplinary cranio-facial resection | No | 54.6 | No | DOD | 13 |
| 11 | 10 | M | C | T4N0M0 | 1 IVA/3 EDX-Adria (Memphis)/ 4 VCR-actino | SD | No | No | No | 60 | 48, prophylactic | Alive without disease/recurrence | 250 |
| 12 | 11 | F | C | T3N0M0 | No | – | No | Cranio-facial resection | No | 60 | No | Alive without disease/recurrence | 100 |
| 13 | 14 | M | C | NA | Yes | NA | No | Endonasal endoscopic resection | Prophylactic | Yes | No | DOD | 44 |
| 14 | 8 | M | C | T3N0M0 | 1 VP16-carboplatin/ 4 CADO | PR | No | Endonasal curettage | No | No | No | DOD | 12 |
| 15 | 16 | M | D | T3N1M0 | 3 VP16-cisplatin | PR | 3 VP16-cisplatin | Multidisciplinary cranio-facial resection | Curative | 58 | 58, curative | DOD | 24 |

(Continues)

**TABLE 1** (Continued)

| Patient | Age (year) | Sex | Kadish (metastatic sites) | Dulguerov TNM staging | Neoadjuvant chemotherapy | Tumor response | Adjuvant chemotherapy | Surgery | Neck dissection | Radiotherapy on primary (Gy) | Cervical radiotherapy (Gy) | Outcome | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | 0.9 | F | D (CSF, BM) | T4N0M1 | 2 VP16-carboplatin/2 IE/2 VDC | PR | No | No | No | No | No | DOD | 5 |
| 17 | 10 | F | D (LN, bone) | T3N1M1 | 3 VP16-carboplatin/2 CADO | PR | No | No | No | No | No | DOD | 9 |
| 18 | 3 | M | D (BM, liver) | T4N0M1 | 1 IVA/1 IVA + VCR J8-J15/3 VP16-carboplatin/2 CADOX | PR | No | No | No | No | No | DOD | 15 |

In accordance with Kadish's criteria (A = tumor limited to the nasal cavity, B = tumor infiltrating the paranasal sinuses, C = tumor extending beyond the nasal cavities and sinuses, D = presence of lymph node or distant metastases) and Dulguerov TNM staging (T1 = tumor involving the nasal cavity and/or paranasal sinuses [excluding sphenoid], sparing the most superior ethmoidal cells, T2 = tumor involving the nasal cavity and/or paranasal sinuses [including the sphenoid] with extension to or erosion of the cribriform plate, T3 = tumor extending into the orbit or protruding into the anterior cranial fossa, without dural invasion, T4 = tumor involving the brain, N0 = no cervical lymph-node metastasis, N1 = any form of cervical lymph node metastasis, M0 = no metastasis, M1 = distant metastasis).

Abbreviations: Adria, adriamycin; BM, bone marrow; CADO, cyclophosphamide-adriamycin-vincristine; CADOX, cyclophosphamide-adriamycin-vincristine-cardioxane; CSF, cerebrospinal fluid; DOD, dead of disease; DOT, dead of toxicity; EDX, cyclophosphamide; IE, ifosfamide-etoposide; IFO, ifosfamide; IVA, ifosfamide-vincristine-D-actinomycin; LN, lymph node; PD, progressive disease; PR, partial response; SD, stable disease; VAI, vincristine-adriamycin-ifosfamide; VCR, vincristine; VDC, vincristine-doxorubicin-cyclophosphamide; VIDE, vincristine-ifosfamide-doxorubicin-etoposide; VP16, etoposide.

**TABLE 2** Clinical signs at diagnosis

| Symptoms[a] | Number of patients |
|---|---|
| Epistaxis | 9 |
| Nasal obstruction | 8 |
| Diplopia/visual disorder | 8 |
| Tumor mass | 8 |
| Exophthalmos | 7 |
| Headache/facial pain | 7 |
| Nausea/vomiting | 5 |
| Hyposmia/anosmia | 2 |
| Chronic rhinitis | 1 |
| Asymptomatic (cranial trauma) | 1 |

[a]Multiple possible.

### 2.1 | Statistical analyses

Event-free survival (EFS) was defined as the interval between the date of diagnosis and the date of progressive disease or relapse. Overall survival (OS) was defined as the interval between the date of diagnosis and date of death or last follow-up. Survival analysis was performed using the Kaplan-Meier method. Time to tumor event outcomes has been calculated from the time of initial diagnosis (first biopsy of initial surgery) to the time of first tumor progression or relapse.

## 3 | RESULTS

### 3.1 | Patient demographics

A total of 18 patients treated in nine different SFCE centers were selected (Table 1). Among them, 10 were male (56%). Median age at diagnosis was 12.2 years (range: 11 months-18 years). Four patients had a personal medical history including type-1 neurofibromatosis, Charcot-Marie-Tooth disease, Willebrand disease, and unspecified malformative congenital syndrome (one case each).

### 3.2 | Clinical characteristics

Clinical signs at diagnosis are summarized in Table 2. Tumor mass mainly involved the inner angle of the eye (five cases) and the hemiface in relation to maxillary sinus involvement (one case). Externalization of tissue mass through the nostril was observed in three patients. Signs of intracranial hypertension were present in four patients. Ophthalmological signs included decreased visual acuity (three cases), third cranial nerve palsy (two cases), ptosis (one case), and fundus papillary edema (one case). Palpable cervical lymphadenopathies occurred in two of 18 patients (11%). The median time from the onset of clinical signs to histological diagnosis was 1.5 months (range: 0.5-36 months).

### 3.3 | Tumor characteristics

At diagnosis, all patients had a diagnostic biopsy of the primary tumor (Table 1). Among them, two patients had concomitant suspected

**TABLE 3** Best response rate to induction chemotherapy (14 patients, one missing data)

| Regimens | Number of patients | Response rate |
|---|---|---|
| CAdO | 3 | 2 PR1 SD |
| CAdO + etoposide-carboplatin | 2 | 2 PR |
| CAdO + etoposide-cisplatin | 1 | PR |
| Ifosfamide-based regimen | 1 | PR |
| Ifosfamide-based regimen + cyclophosphamide-adriamycin | 1 | SD |
| Ifosfamide-based regimen + cyclophosphamide-adriamycin + vincristine-actinomycin D | 1 | SD |
| Ifosfamide-based regimen + etoposide-carboplatin + CAdO | 1 | PR |
| Etoposide-carboplatin | 1 | PR |
| Etoposide-cisplatin | 1 | PR |
| Etoposide-carboplatin + ifosfamide-etoposide + vincristine-adriamycin-cyclophosphamide | 1 | PR |

Abbreviations: CAdO, cyclophosphamide-adriamycin-vincristine; PR, partial response; SD, stable disease.

cervical lymph node samples (one adenectomy, one fine needle aspiration) showing the malignant tumor proliferation of undifferentiated cells. One patient had a Hyams grade-I, three patients a grade-II, six patients a grade-III, and six patients a grade-IV tumor (missing data in two cases).

One tumor extension was classified as a Kadish stage A (6%), three stage B (17%), 10 stage C (55%), and four stage D (22%) (Table 1; Figure S1). Two patients had distant metastases: osteomedullar tumor invasion combined with hepatic metastases (one case) and diffuse malignant meningitis (one case) without cervical lymph node invasion. Among five patients with a cerebrospinal fluid analysis, one patient had meningeal tumor spread.

Eleven patients had tumors evaluated between 5 and 10 cm and six had smaller than 5 cm (missing data in one case). Seven had an initial fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (FDG-PET-CT) tumor assessment. The average maximum standardized uptake value (SUV) for the primary tumor was 9.4 (range: 5.2-15.3). One patient with cervical metastases at diagnosis had a maximum SUV of 16.6 on nodes (maximum SUV on primary tumor was 15.3). Patients with distant metastases did not have an FDG-PET-CT evaluation.

## 3.4 | Chemotherapy

Overall, 14 of 18 patients received neoadjuvant chemotherapy (Table 1). Delivered chemotherapy regimens are summarized in Table 3. Ten out of 13 patients (77%) had an objective response to induction chemotherapy, including 83% (five of six cases) after cyclophosphamide-adriamycin-oncovin–based, 50% after ifosfamide-based (two of four cases), and 100% after cisplatinum-based regimens (three of three cases).

At the end of neoadjuvant chemotherapy, three patients developed early progressive disease with neuromeningeal involvement and received second-line therapy (one case) or immediate palliative care (two cases). One patient with a delayed diagnosis and altered general status received exclusive palliative chemotherapy (patient no. 6).

## 3.5 | Local treatment

Fourteen patients received local therapy (Table 1). Tumor resection was performed for 12 patients, whereas six patients did not have any surgery due to early progression (four cases), exclusive local RT (one case), and parental refusal (one case) during first-line therapy. For three patients, immediate surgery at diagnosis was performed at diagnosis. A complete craniofacial resection (CFR) was performed for one patient with a Kadish C (orbital extension)/Hyams II tumor after para-lateronasal incision. One patient with Kadish A/Hyams II tumor had an endoscopic endonasal resection (EER) and another patient with Kadish B/Hyams I tumor had CFR. These two latter resections were microscopically incomplete. For the nine other patients, surgery was performed after neoadjuvant chemotherapy by CFR alone (one case) or combined with a craniotomy (two cases) and through isolated EER (three cases) combined with a craniotomy (three cases). Overall, the primary resection was microscopically complete in only three of 12 cases (one CFR and two EER) and incomplete in eight of 12 cases (four CFR, four EER, missing data in one case).

Among the two patients with cervical lymph node metastases, one patient had a neck dissection and one patient did not due to early disease progression.

Locoregional treatment included RT in 11 patients (exclusive, two cases; after surgery, nine cases) and seven did not have RT for various reasons (early progression, five cases; complete resection or physician decision, one case each). The average dose delivered to the primary site was 56.3 Gy (range: 54-60 Gy) with a median dose per fraction of 2 Gy (range: 1.8-2 Gy) and a median number of fractions of 29 (range: 24-33). Two patients received irradiation of the cervical chains at 54 and 48 Gy for initial nodal involvement and prophylactic treatment, respectively.

## 3.6 | Adjuvant therapies

Among the 14 patients with local therapy, four received adjuvant chemotherapy after surgery and RT (three cases) or exclusive RT (one case). Ten patients did not receive adjuvant therapy due to early progression (one case), physician decision (two cases), complete

remission (CR) after surgery (one case), and CR after surgery and RT (six cases).

### 3.7 | Outcome

After first-line therapy, 13 of 18 patients were in CR. Ten patients had local progression combined with a meningeal regional progression in six, without nodal or distant relapse. All patients with tumor events died despite further lines of therapy. Overall median time from tumor event to death was 2.5 months (range, 1 day-14 months). For leptomeningeal relapse, this delay was 3.1 months (range, 0.03-14.1) and 2.5 months when a local relapse occurred (range, 1.3-12.4). To note, among the four patients with local relapse, two patients had a subsequent tumor event with loco-regional tumor progression including leptomeningeal involvement. Among the three patients with early progression, all tumor progressions occurred soon after neoadjuvant chemotherapy before the start of the local therapy, despite a very good partial response to initial chemotherapy (Table 4).

After a median follow-up of 7.6 years (range, 3.8-17.9), eight patients survived and both 5-year OS and EFS are 44.4% (±11.7%). The median time of tumor events was 4.5 months (range, 3.1-20.4) (Figure 1A and B). Patients with high-stage tumors (Kadish C/D) have a significantly worse prognosis than patients with low-stage tumors (Kadish A/B), 5-year OS 100.0% versus 28.6 ± 12.1% (log-rank $P = .032$) (Figure 1C). There were no long-term survivors in Kadish D patients. Outcome of patients with high-grade tumors (Hyams III/IV) was significantly worse than patients with low-grade tumors (Hyams I/II), 5-year OS 100.0% versus 25.0% (±12.5%) (log-rank $P = .026$) (Figure 1D).

### 3.8 | Sequelae

Total therapy burden for the eight survivors represented chemotherapy (five cases), primary RT (eight cases), cervical RT (one case, prophylactic), and local surgery (six cases). Among the six survivors treated with surgery, three patients had chronic grade-3 sinus disorders. Long-term complications included olfactory nerve damage with anosmia (five cases, including one grade II and four grade III). All of them were treated with surgery and RT and only one received platinum-based chemotherapy. A grade-3 cataract was present in four patients. Of the eight survivors with a follow-up of more than 2 years, four had CTCAE grade 3 cataract, three had dry eyes with one grade 3 keratitis, one had grade 3 postradiation retinopathy, and one had grade 3 extraocular muscle paresis.

## 4 | DISCUSSION

There is currently no consensual reference treatment for pediatric ENB because of the rarity of this tumor during childhood. Local ENB standard treatment in adults is extensive surgery followed by radiation therapy. Open CFR was the main approach especially for extended tumors and an endoscopic approach was reserved for limited low-stage tumors. However, EER showed better local control, better survival, and less morbidity.[25] In a recent study, stage-matched patients had a better survival with an endoscopic approach than open surgery especially in Kadish C patients.[26] In our series, seven patients were treated with EER resulting only in two complete histological resections. Hence, EER is promising especially in children in order to decrease the morbidity of CFR, but clinicians also have to focus on occult dural involvement that may be the origin of relapse.[27] In case of an intracranial invasion at diagnosis, an endoscopic approach needs to be supplemented with a craniotomy to treat the intracranial component. Indeed, in patients with sinonasal malignancies eroding the bony anterior skull base without evidence of dural involvement on preoperative imaging, the occult rate of dural invasion has been estimated as high as 54%, independent of any surgical technique.[28] Additionally, dural resection significantly improved margin control and survival exclusively in the ENB cohort.[28] Interestingly, the poor prognosis of ENB in children is mainly related to neuromeningeal dissemination in our series. Indeed, six patients developed leptomeningeal metastases during the first relapse and a total of eight patients had leptomeningeal localization during the course of the disease. The anatomic characteristics of ENB may facilitate neuromeningeal dissemination by an occult involvement of the dura mater. Neoplastic meningitis harbors a poor prognosis as in various cancer types.[29–31] ENB leptomeningeal dissemination at relapse is already described in adult population even after a long period of remission and has a bad prognosis.[32–34] We recommend postcontrast T1 and T2 Flair with axial, coronal, and sagittal sequences to assess intradural extension and leptomeningeal dissemination at diagnosis and at relapse.

RT is also another cornerstone of the ENB local treatment. It enables local control with doses between 45 and 65 Gy in pediatric patients.[1,3,6] RT is mainly used in a postoperative setting, but may also provide a good response in a neoadjuvant setting.[35] RT combined with neoadjuvant chemotherapy shows significant tumor volume reduction in patients with an extended unresectable tumor, which allows for complete resection under better conditions.[36] Therefore, RT seems to be effective for ENB local control and may prevent dural tumor recurrence. New radiation techniques, like proton beam therapy, may limit long-term toxicity illustrated by reported studies showing a good local control with less adverse effects but the risk to have to limited margins is real.[37,38]

ENB tumor extension is commonly described according to the modified Kadish classification.[9,10] Pediatric patients usually present with a more advanced staged disease than adults.[1,5] Our results are in agreement as 78% of patients are presented with Kadish C or D tumors. The only Kadish A tumor in our series was related to an early incidental diagnosis (brain computed tomography [brain-CT] scan performed for cranial trauma). In adults, this staging system remains a significant predictor of survival.[39–42] Our results confirmed this observation showing that patients with high-stage tumors (Kadish C-D) have a significantly worse prognosis than patients with low-stage tumors (Kadish A-B), 5-year OS 100.0% versus 28.6 ± 12.1% (log-rank $P = .032$). However, the relevance of a modified Kadish classification is still under debate.[39–43] Indeed, Kadish C tumors constitute a very heterogeneous group related by their extension beyond paranasal sinuses, but

**TABLE 4** Main pediatric series in the literature

| Reference [Year of publication] | Number of patients | Median Age(range) | Sex | Kadish | First-line treatment | Median follow-up | Survivals |
|---|---|---|---|---|---|---|---|
| Venkatramani et al [2016] | 24 | 14 years (0.6-20) | F = 18<br>M = 6 | B = 8<br>C = 8<br>D = 8 | S + RT = 10<br>Neo CT + RT = 6<br>Neo CT + S + RT = 5<br>Neo CT = 1<br>S = 1<br>Neo CT + S = 1 | NA | 5-year EFS 73.7% (50.5-87.3%)<br>5-year OS 72.8% (46-87.9%) |
| Lucas et al [2015] | 8 | 10 years (4-21) | F = 6<br>M = 2 | B = 3<br>C = 1<br>D = 4 | Neo CT + RT = 2<br>S + RT = 2<br>Neo CT + S + Adj CT + RT = 2<br>S + RT + Adj CT = 1<br>Neo CT + S = 1 | 4.6 years (0.8-9.4) | 5-year OS 87.5% |
| Kababri et al [2014] | 11 | 14 years (0.8-18) | F = 8<br>M = 3 | B = 5<br>C = 6 | Neo CT + S + RT = 7<br>S + RT = 1<br>S + Adj CT + RT = 1<br>Neo CT + S + Adj CT + RT = 1 | 8.8 years (3.8-16.4) | 5-year EFS 91% (62-98%)<br>5-year OS 91% (62-98%) |
| Bisogno et al [2012] | 9 | 9.9 years (0.9-18) | F = 3<br>M = 6 | B = 3<br>C = 6 | CT + S + RT = 5<br>CT + RT = 3<br>S + CT = 1 | 13.4 years (9.2-22.9) | 5-year EFS 77.8% (36.6-93.9%)<br>5-year OS 88.9% (43.3-98.4%) |
| Eich et al [2005] | 19 | 14 years (5-20) | F = 10<br>M = 9 | B = 4<br>C = 15 | S + RT + CT = 7<br>CT + S + RT = 5<br>S = 4<br>RT + CT = 2<br>S + RT = 1 | 3.1 years (0.3-23) | 5-year EFS 55% (±13%)<br>5-year OS 73% (±12%) |
| Kumar et al [2002] | 5 | 13 years (5-16) | F = 1<br>M = 4 | A = 1<br>B = 1<br>C = 3 | CT + RT = 2<br>CT = 1<br>CT + S = 1<br>CT + S + RT = 1 | NA | NA |
| This study [2020] | 18 | 12.2 years (0.9-18) | F = 8<br>M = 10 | A = 1<br>B = 3<br>C = 10<br>D = 4 | Neo CT = 4<br>Neo CT + S + RT = 4<br>Neo CT + S + Adj CT + RT = 3<br>S + RT = 3<br>Neo CT + S = 2<br>Neo CT + RT = 1<br>Neo CT + RT + Adj CT = 1 | 2.4 years (0.3-17.9) | 5-year EFS 44.4% (±11.7%)<br>5-year OS 44.4% (±11.7%) |

Abbreviations: Adj CT, adjuvant chemotherapy; CT, chemotherapy; EFS, event-free survival; F, female; M, male; NA, not available; Neo CT, neoadjuvant chemotherapy; OS, overall survival; RT, radiotherapy; S, surgery.

without discrimination regarding involved anatomic sites.[39–42] In our study, we observed 10 local recurrences in the initial Kadish C tumor with involvement of the anterior cerebral fossa and, among them, six with meningeal progressions. The risk of a locoregional leptomeningeal recurrence may be explained by the anatomic connection between paranasal sinuses and leptomeningeal spaces through the cribriform plate. Dulguerov et al proposed a TNM-based classification that correlates with outcomes.[11] This staging system takes into account the early involvement of the cribriform plate in stage T2 and separates the extradural intracranial extension from the invasion of the cranial frontal lobe.[12,41,42] A better assessment of skull base involvement may predict the risk of recurrence using the Dulguerov staging system.

ENB belongs to the family of small round blue cell tumors in the nasal cavities and paranasal sinuses, characterized by a wide morphological heterogeneity. Hyams grading classifies ENB into four histopathological grades defined by its degree of differentiation.[44] High-grade tumors are associated with a high relapse incidence and poor disease-free survival.[45,46] In our series, 12 of 18 patients had high-grade tumors and Hyams grading correlated also to outcome. Moreover, all patients with low-grade tumors were long-term survivors. Kumar et al reported the same high proportion of high-grade tumors in children (six of eight patients with Hyams III or IV).[4] Interestingly, adult ENB is more frequently classified as low-grade tumors with up to 78% of Hyams I or II tumors.[14] This observation may explain the more aggressive biological behavior of ENB during childhood and the poor survival in our series. A recent study found that half of ENBs have clinically relevant genomic alteration, which are identified in different genes such as *TP53*, *PIK3CA*, *NF1*, *CDKN2A*, or *CDKN2C*.[47–49] Recently, Classe et al reported an integrative multiomics analysis of ENB identifying two subgroups of ENBs: neural and basal.[50] They showed that the basal-like subgroup includes poorly differentiated tumors with a high expression of embryonic genes and a shorter survival for patients sharing some similarities with our cohort of pediatric ENBs (poor survival, dedifferentiated tumor, high Ki67). Interestingly, basal-like ENBs harbor *IDH2* mutations in one-third of cases that might represent a therapeutic option.[50,51]

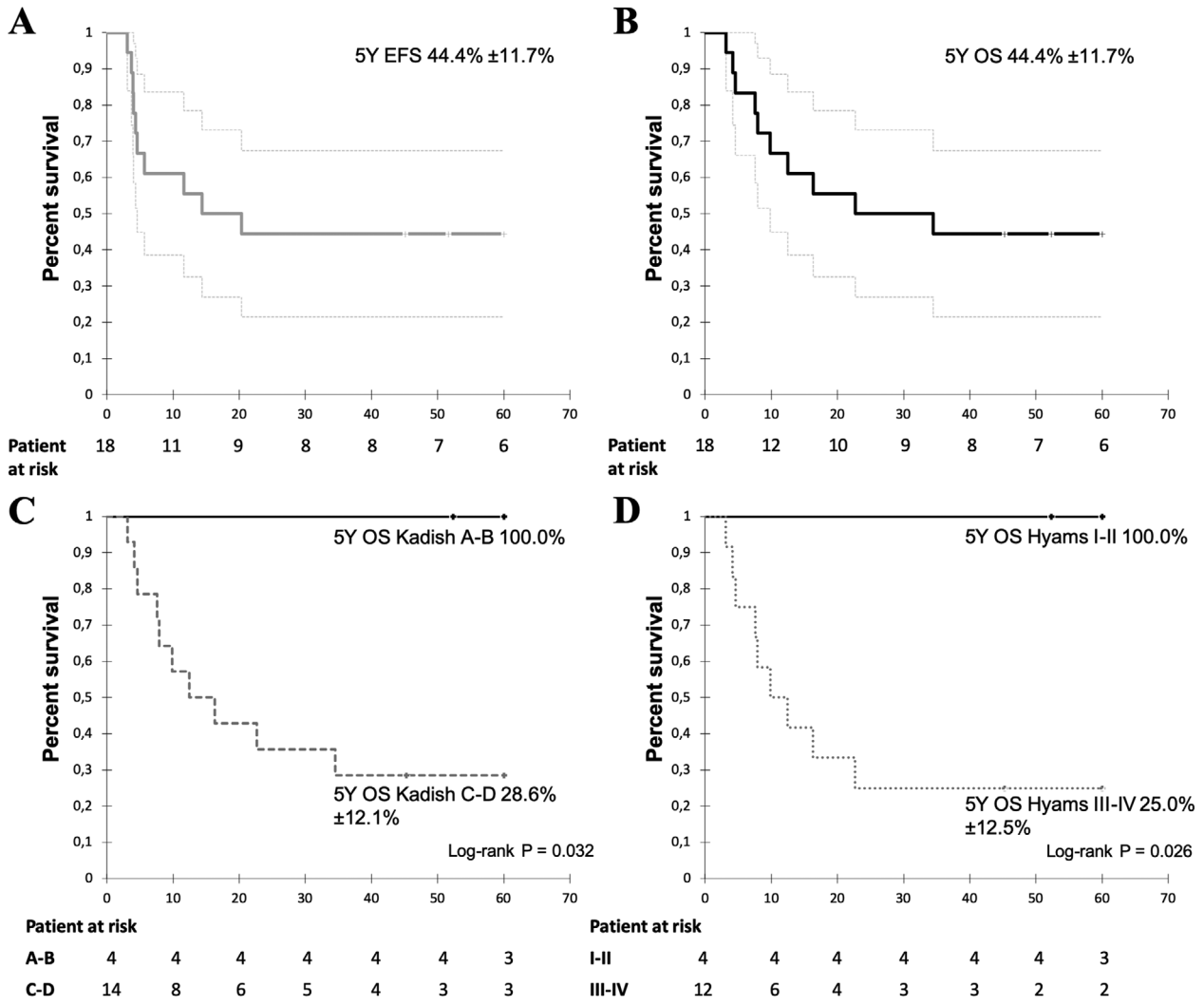


**FIGURE 1** Outcome of the population of patients with ENB according to initial tumor extension and histological grade. A, Event-free survival of the whole population (n = 18). The gray dotted curves represent 95% confidence intervals. B, Overall survival of the whole population (n = 18). The gray dotted curves represent 95% confidence intervals. C, Outcome of patients according to the Kadish tumor extension (n = 18 pts): low stages (Kadish A-B) versus high stages (Kadish C-D). D, Outcome of patients according to a histological grade (n = 16 pts): low grades (Hyams I-II) versus high grades (Hyams III-IV)

Lymph node involvement is present in 10% of adult ENB patients at diagnosis and increases to 20-30% during the course of the disease.[22,52] In previous published pediatric studies (Table 5), lymph node involvement at diagnostic was more frequent and concerns approximately 25% of patient.[1,3] In our series, only two of 18 patients were diagnosed with cervical lymph node metastases at diagnosis, even if this rate might be underestimated as only seven of 18 patients were assessed by an FDG-PET-CT at diagnosis. Banuchi et al described the pattern of regional nodes metastases in adult ENB, which mainly occurred in level II (88%), level I (50%), level III (50%), level IV (38%), and retropharyngeal level (25%).[53] One adult study evaluated the utility of an FDG-PET-CT in ENB staging and quantified the additional benefit of an FDG-PET-CT to conventional imaging. They showed that an FDG-PET-CT modified disease staging or changed clinical management in 39% of patients. The more frequent restaging concerned the involvement of cervical node metastases in almost 20% of patients.[54] Cervical node metastases are associated with poor survival in adults.[20,55] Treatment strategy is consensual for adult patients with cervical node metastases and is based on systematic neck dissection with cervical radiation therapy.[21] The 2 N1-patients in our cohort had a poor prognosis without long-term survival. Precise assessment of cervical lymph nodes at diagnosis is therefore critical. Nodal staging requires a thorough clinical and radiological examination and any suspicious node should lead to a cytological or pathological confirmation. The role of systematic CPNI in patients with an N0 tumor is still under debate. Some authors claim that CPNI reduces the risk of cervical node recurrence, but without benefits regarding survival, while others argue that CPNI plays a limited role in preventing cervical nodal failure.[56,57] Although frequently described in adult series,[58] we did not observe a relapse in initially uninvolved cervical lymph nodes.

The role of chemotherapy in ENB treatment strategy remains unclear. Neoadjuvant therapy may reduce the tumor burden in

**TABLE 5** Characteristics of second-line therapy after relapse for ENB patients

| | First relapse/progression | | | Second tumor event | | | | Status at the last follow-up |
|---|---|---|---|---|---|---|---|---|
| Patient number | Time from last treatment (days) | Site | Treatment (number of cycles) | Time from last treatment (days) | Relapse (R)/progression (P) | Site of relapse | Treatment | Time from first tumor event (days) |
| 6 | Palliative treatment at diagnosis with two courses of oral etoposide and one course of cyclophosphamide | | | | | | | DOD (90) |
| 8 | 69<br>Off therapy | Local (anterior cranial fossa) | CAdO (1) | NA | NA | NA | NA | DOT (39) |
| 9 | 53<br>Off therapy | Local (anterior cranial fossa) | Chemotherapy (CAdO (2)/VP16-Carbo (2), surgery with craniotomy, radiotherapy (59.4 Gy) | 25 | R | Leptomenigeal with spinal metastasis + bone | Palliative | DOD (372) |
| 10 | 71<br>Off therapy | Local (anterior cranial fossa) + Leptomeningeal | Palliative | NA | NA | NA | NA | DOD (24) |
| 13 | 613 (from diagnostic) | Leptomeningeal with epidural involvement | VP16-Carbo<br>Intrathecal chemotherapy<br>Radiotherapy | NA | NA | NA | NA | DOD (422) |
| 14 | 1<br>On therapy | Local (anterior cranial fossa) + Leptomeningeal | Thiotepa HD (Phase II)<br>Radiotherapy (48.6 Gy) | 21 | P | Bone + bone marrow | Palliative | DOD (164) |
| 15 | 294<br>Off therapy | Local (anterior cranial fossa) + Leptomeningeal | VP16-Carbo (6)<br>EDX-Adria (3) | 47 | P | Leptomeningeal progression | Palliative | DOD (228) |
| 16 | 7<br>On therapy | Local (anterior cranial fossa) + Leptomeningeal | Palliative | NA | NA | NA | NA | DOD (5) |
| 17 | 24<br>On therapy | Local (anterior cranial fossa) | VIP (2)<br>Radiotherapy (60 Gy) | 1<br>On therapy (41 Gy) | P | Spinal cord compression | Palliative irradiation | DOD (113) |
| 18 | 1<br>On therapy | Leptomeningeal | Palliative | NA | NA | NA | NA | DOD (1) |

Abbreviations: Adria, adriamycin; CADO, cyclophosphamide-adriamycin-vincristine; Carbo, carboplatin; DOD, dead of disease; DOT, dead of toxicity; EDX, cyclophosphamide; IE, ifosfamide-etoposide; Ifo, ifosfamide; IVA, ifosfamide-vincristine-D-actinomycin; NA, not available; VDC, vincristine-doxorubicin-cyclophosphamide; VP16, etoposide; VIP, VP16-ifosfamide-cisplatin.

order to facilitate the achievement of negative surgical margins and improve survival outcomes. Our results confirm that ENB is a chemosensitive tumor with a best overall response rate of 77% (10 of 13 patients). In adults, chemotherapy is recommended in cases of high-grade and positive margins tumors, unresectable tumors, metastatic disease, and relapses.[59] Response rate to neoadjuvant chemotherapy is higher in a Hyams high-grade group compared to a Hyams low-grade group, 78% versus 50%, respectively.[17] Furthermore, Polin et al showed that patients with a response to neoadjuvant therapy with chemotherapy and/or RT have a significant lower rate of disease-related mortality.[35] In a pediatric series, due to the initial tumor spread, neoadjuvant chemotherapy is widely applied using neuroblastoma- or rhabdomyosarcoma-based protocols[2,3,6] (Table 5).

In summary, as in adults, the survival of ENB in children seems related to the Hyams grade, Kadish and N stages. There is currently no standard treatment, and the overall strategy should always be defined by specialized multidisciplinary teams including a pediatric oncologist, ENT surgeon, neurosurgeon, and radiotherapist. Our recommendation is to deliver neoadjuvant chemotherapy followed by local treatment with surgery and RT. Due to the possibility of early progression in such disease, a dose intensity schedule seems necessary soon after diagnosis to avoid long breaks and early tumor resistance development. The incidence of this exceptional disease requires international collaboration, such as the one conducted by the *European Cooperative Study Group for Pediatric Rare Tumors* (EXPeRT) group.[60] The main goal of this collaborative initiative is to share experiences on a very rare tumor type in children, collaborate with medical oncologists, and propose harmonious therapeutic guidelines in order to improve clinical and biological knowledge as well as patient outcomes.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ACKNOWLEDGMENT

The French Fracture database is supported by the “Enfant, cancers et santé” association that did not take part in any of the analyses in this manuscript.

## ORCID

*Benoît Dumont* https://orcid.org/0000-0001-8331-3480
*Brice Fresneau* https://orcid.org/0000-0001-7603-7828
*Anne-Sophie Defachelles* https://orcid.org/0000-0002-4277-9871
*Hervé J Brisse* https://orcid.org/0000-0003-2794-5875
*Daniel Orbach* https://orcid.org/0000-0002-2520-139X

## REFERENCES

1. Venkatramani R, Pan H, Furman WL, et al. Multimodality treatment of pediatric esthesioneuroblastoma. *Pediatr Blood Cancer*. 2016;63(3):465-470.
2. Lucas JT, Ladra MM, MacDonald SM, et al. Proton therapy for pediatric and adolescent esthesioneuroblastoma: proton radiotherapy for esthesioneuroblastoma. *Pediatr Blood Cancer*. 2015;62(9):1523-1528.
3. Bisogno G, Soloni P, Conte M, et al. Esthesioneuroblastoma in pediatric and adolescent age. A report from the TREP project in cooperation with the Italian Neuroblastoma and Soft Tissue Sarcoma Committees. *BMC Cancer*. 2012;12(1):117.
4. Kumar M, Fallon RJ, Hill JS, Davis MM. Esthesioneuroblastoma in children. *J Pediatr Hematol Oncol*. 2002;24(6):482-487.
5. Eich HT, Müller R-P, Micke O, Kocher M, Berthold F, Hero B. Esthesioneuroblastoma in childhood and adolescence: better prognosis with multimodal treatment. *Strahlenther Onkol*. 2005;181(6):378-384.
6. Kababri ME, Gaspar N, Dufour C, Oberlin O. Esthesioneuroblastoma in children and adolescent: experience on 11 cases with literature review. *J Pediatr Hematol Oncol*. 2014;36(2):5.
7. Benoit MM, Bhattacharyya N, Faquin W, Cunningham M. Cancer of the nasal cavity in the pediatric population. *Pediatrics*. 2008;121(1):e141-e145.
8. Hyams VJ, Batsakis JG, Michaels L. Tumors of the Upper Respiratory Tract and Ear. Washington, DC: Armed Forces Institute of Pathology; 1988.
9. Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer*. 1976;37(3):1571-1576.
10. Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. *Neurosurgery*. 1993;32(5):706-714. discussion 714-715.
11. Dulguerov P, Calcaterra T. Esthesioneuroblastoma: the UCLA experience 1970–1990. *Laryngoscope*. 1992;102(8):843-849.
12. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. *Lancet Oncol*. 2001;2(11):683-690.
13. Devaiah AK, Andreoli MT. Treatment of esthesioneuroblastoma: a 16-year meta-analysis of 361 patients. *Laryngoscope*. 2009;119(7):1412-1416.
14. Tajudeen B, Arshi A, Suh J, et al. Esthesioneuroblastoma: an update on the UCLA Experience, 2002–2013. *J Neurol Surg Part B Skull Base*. 2014;76(01):043-049.
15. Zafereo ME, Fakhri S, Prayson R, et al. Esthesioneuroblastoma: 25-year experience at a single institution. *Otolaryngol-Head Neck Surg*. 2008;138(4):452-458.
16. Bachar G, Goldstein DP, Shah M, et al. Esthesioneuroblastoma: the Princess Margaret Hospital experience. *Head Neck*. 2008;30(12):1607-1614.
17. Su SY, Bell D, Ferrarotto R, et al. Outcomes for olfactory neuroblastoma treated with induction chemotherapy. *Head Neck*. 2017;39(8):1671-1679.
18. Bartel R, Gonzalez-Compta X, Cisa E, et al. Importance of neoadjuvant chemotherapy in olfactory neuroblastoma treatment: series report and literature review. *Acta Otorrinolaringol Engl Ed*. 2018;69(4):208-213.
19. Miller KC, Marinelli JP, Van Gompel JJ, et al. Utility of adjuvant chemotherapy in patients receiving surgery and adjuvant radiotherapy for primary treatment of esthesioneuroblastoma. *Head Neck*. 2019;41(5):1335-1341.
20. Naples JG, Spiro J, Tessema B, Kuwada C, Kuo C-L, Brown SM. Neck recurrence and mortality in esthesioneuroblastoma: implications for management of the N0 neck: neck Recurrence and Mortality in ENB. *Laryngoscope*. 2016;126(6):1373-1379.
21. Zanation AM, Ferlito A, Rinaldo A, et al. When, how and why to treat the neck in patients with esthesioneuroblastoma: a review. *Eur Arch Otorhinolaryngol*. 2010;267(11):1667-1671.
22. Howell MC, Branstetter BF, Snyderman CH. Patterns of regional spread for esthesioneuroblastoma. *Am J Neuroradiol*. 2011;32(5):929-933.
23. Réguerre Y, Lacour B, André N, et al. Epidemiology and management of rare paediatric tumours within the framework of the French Society for Children Cancer. *Bull Cancer*. 2010;97(9):1041-1045.

24. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
25. Gallia GL, Asemota AO, Blitz AM, et al. Endonasal endoscopic resection of olfactory neuroblastoma: an 11-year experience. *J Neurosurg*. 2018:1-7. doi:10.3171/2018.2.JNS171424
26. Harvey RJ, Nalavenkata S, Sacks R, et al. Survival outcomes for stage-matched endoscopic and open resection of olfactory neuroblastoma. *Head Neck*. 2017;39(12):2425-2432.
27. Yu Y, El-Sayed IH, McDermott MW, et al. Dural recurrence among esthesioneuroblastoma patients presenting with intracranial extension: dural recurrence of esthesioneuroblastoma. *Laryngoscope*. 2018;128:2226-2233.
28. Ziai H, Yu E, Fu T, et al. Impact of dural resection on sinonasal malignancies with skull base encroachment or erosion. *J Neurol Surg Part B Skull Base*. 2018;79(05):419-426.
29. Graber JJ, Kesari S. Leptomeningeal metastases. *Curr Treat Options Oncol*. 2018;19(1). https://doi.org/10.1007/s11864-018-0518-0.
30. Grisold W, Grisold A. Cancer around the brain. *Neuro-Oncol Pract*. 2014;1(1):13-21.
31. Brower JV, Saha S, Rosenberg SA, Hullett CR, Ian Robins H. Management of leptomeningeal metastases: prognostic factors and associated outcomes. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2016;27:130-137.
32. Martinez-Perez R, Hardesty D, Palmer J, et al. Remote leptomeningeal dissemination in olfactory neuroblastoma mimicking multiple parasagittal meningiomas: a diagnostic and therapeutic challenge. *World Neurosurg*. 2019;134:361-364.
33. Saito A, Sasaki T, Inoue T, et al. Non-contiguous meningeal recurrence of olfactory neuroblastoma: a case report and literature review. *NMC Case Rep J*. 2018;5(3):69-72.
34. Sivakumar W, Oh N, Cutler A, Colman H, Couldwell W. Cranial and spinal leptomeningeal dissemination in esthesioneuroblastoma: two reports of distant central nervous system metastasis and rationale for treatment. *Surg Neurol Int*. 2015;6(26):628.
35. Polin RS, Sheehan JP, Chenelle AG, et al. The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: the University of Virginia experience. *Neurosurgery*. 1998;42(5):1029-1037.
36. Sohrabi S, Drabick JJ, Crist H, Goldenberg D, Sheehan JM, Mackley HB. Neoadjuvant concurrent chemoradiation for advanced esthesioneuroblastoma: a case series and review of the literature. *J Clin Oncol*. 2011;29(13):e358-e361.
37. Nishimura H, Ogino T, Kawashima M, et al. Proton-beam therapy for olfactory neuroblastoma. *Int J Radiat Oncol Biol Phys*. 2007;68(3):758-762.
38. Nakamura N, Zenda S, Tahara M, et al. Proton beam therapy for olfactory neuroblastoma. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2017;122(3):368-372.
39. Yin Z, Wang Y, Wu Y, et al. Age distribution and age-related outcomes of olfactory neuroblastoma: a population-based analysis. *Cancer Manag Res*. 2018;10:1359-1364.
40. Jethanamest D, Morris LG, Sikora AG, Kutler DI. Esthesioneuroblastoma: a population-based analysis of survival and prognostic factors. *Arch Otolaryngol Neck Surg*. 2007;133(3):276-280.
41. Schwartz JS, Palmer JN, Adappa ND. Contemporary management of esthesioneuroblastoma. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24(1):63-69.
42. Dublin A, Bobinski M. Imaging characteristics of olfactory neuroblastoma (esthesioneuroblastoma). *J Neurol Surg Part B Skull Base*. 2015;77(01):001-005.
43. Joshi RR, Husain Q, Roman BR, et al. Comparing Kadish, TNM, and the modified Dulguerov staging systems for esthesioneuroblastoma. *J Surg Oncol*. 2019;119(1):130-142.
44. Saade RE, Hanna EY, Bell D. Prognosis and biology in esthesioneuroblastoma: the emerging role of Hyams grading system. *Curr Oncol Rep*. 2015;17(1):423.
45. Bell D, Saade R, Roberts D, et al. Prognostic utility of Hyams histological grading and Kadish-Morita staging systems for esthesioneuroblastoma outcomes. *Head Neck Pathol*. 2015;9(1):51-59.
46. Van Gompel J, Giannini C, Olsen K, et al. Long-term outcome of esthesioneuroblastoma: Hyams grade predicts patient survival. *J Neurol Surg Part B Skull Base*. 2012;73(05):331-336.
47. Gay LM, Kim S, Fedorchak K, et al. Comprehensive genomic profiling of esthesioneuroblastoma reveals additional treatment options. *Oncologist*. 2017;22(7):834-842.
48. Wang L, Ding Y, Wei L, et al. Recurrent olfactory neuroblastoma treated with cetuximab and sunitinib: a case report. *Medicine*. 2016;95(18):e3536.
49. Czapiewski P, Kunc M, Haybaeck J. Genetic and molecular alterations in olfactory neuroblastoma—implications for pathogenesis, prognosis and treatment. *Oncotarget*. 2016;7(32):52584-52596.
50. Classe M, Yao H, Mouawad R, et al. Integrated multi-omic analysis of esthesioneuroblastomas identifies two subgroups linked to cell ontogeny. *Cell Rep*. 2018;25(3):811-821.e5.
51. Capper D, Engel NW, Stichel D, et al. DNA methylation-based reclassification of olfactory neuroblastoma. *Acta Neuropathol*. 2018;136(2):255-271.
52. Thompson LDR. Olfactory neuroblastoma. *Head Neck Pathol*. 2009;3(3):252-259.
53. Banuchi VE, Dooley L, Lee NY, et al. Patterns of regional and distant metastasis in esthesioneuroblastoma: metastatic disease in esthesioneuroblastoma. *Laryngoscope*. 2016;126(7):1556-1561.
54. Broski SM, Hunt CH, Johnson GB, Subramaniam RM, Peller PJ. The added value of 18F-FDG PET/CT for evaluation of patients with esthesioneuroblastoma. *J Nucl Med*. 2012;53(8):1200-1206.
55. Li R, Tian S, Zhu Y, et al. Management of orbital invasion in esthesioneuroblastoma: 14 years' experience. *Radiat Oncol*. 2019;14(1). https://doi.org/10.1186/s13014-019-1313-1.
56. Jiang W, Mohamed ASR, Fuller CD, et al. The role of elective nodal irradiation for esthesioneuroblastoma patients with clinically negative neck. *Pract Radiat Oncol*. 2016;6(4):241-247.
57. Noh OK, Lee S, Yoon SM, et al. Radiotherapy for esthesioneuroblastoma: is elective nodal irradiation warranted in the multimodality treatment approach. *Int J Radiat Oncol*. 2011;79(2):443-449.
58. Kuan EC, Nasser HB, Carey RM, et al. A population-based analysis of nodal metastases in esthesioneuroblastomas of the sinonasal tract: esthesioneuroblastoma nodal metastasis patterns. *Laryngoscope*. 2018;129:1025-1029.
59. Abdelmeguid AS. Olfactory neuroblastoma. *Curr Oncol Rep*. 2018;20(1):7.
60. Bisogno G, Ferrari A, Bien E, et al. Rare cancers in children—The EXPeRT initiative: a report from the European Cooperative Study Group on Pediatric Rare Tumors. *Klin Padiatr*. 2012;224(6):416-420.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Dumont B, Fresneau B, Claude L, et al. Pattern of loco-regional relapses and treatment in pediatric esthesioneuroblastoma: The French very rare tumors group (*Fracture*) contribution. *Pediatr Blood Cancer*. 2020;e28154. https://doi.org/10.1002/pbc.28154