Esthesioneuroblastoma in Childhood and Adolescence

Better Prognosis with Multimodal Treatment?* **

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Background and Purpose: Only 3% of all malignant intranasal tumors are esthesioneuroblastomas (ENB) and only 20% of these rare neuroectodermal tumors are diagnosed up to 20 years of age. Radiotherapy and surgery are established treatment modalities for these patients, but the role of chemotherapy, especially in a multimodal approach, is not well defined. To investigate the influence of radio- and chemotherapy, the treatment and course of the disease in children and adolescents with ENB were analyzed retrospectively.

Patients and Methods: 19 unselected patients (nine male and ten female) diagnosed with ENB ≤ 20 years of age were included in this analysis. Median age at diagnosis was 14.0 years (range, 5–20 years). The tumors were Kadish stage B in 4/19 patients and stage C in 15/19 patients. 17 patients underwent surgery, either without further therapy (n = 4), followed by radiotherapy (n = 1) or as part of multimodal regimens (n = 12). Two patients received radio- and chemotherapy without surgery. Complete resection (R0) was achieved in 15 out of 17 patients with surgery including all five patients with preoperative chemotherapy due to unresectable primary at diagnosis.

Results: The 5-year overall survival (OS) for the whole group was 73% ± 12% and the 5-year event-free survival (EFS) 55% ± 13%. None of the four patients with stage B experienced tumor progression so far, whereas seven out of 15 patients with stage C did (5-year EFS 47% ± 14%; not significant). Patients with Kadish stage C and multimodal treatment strategies combing surgery, chemo- and radiotherapy had a significantly better outcome than patients with stage C and less than three treatment modalities (65% ± 17% vs. 20% ± 18%; p = 0.02).

Conclusion: These data indicate a benefit of multimodal treatment regimens combining surgery, chemo- and radiotherapy for pediatric patients with ENB Kadish stage C. Chemotherapy appears to improve resectability, EFS, and OS. Radiotherapy is an integral part in the management of children and young adolescents with ENB in Kadish stage B and C.

Key Words: Pediatric esthesioneuroblastoma · Olfactory neuroblastoma · Radiotherapy · Multimodality therapy · Chemotherapy

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Ästhesioneuroblastom im Kindes- und Jugendalter. Verbesserte Prognose durch multimodale Behandlungsansätze?

Hintergrund und Ziel: Das Ästhesioneuroblastom macht lediglich 3% aller intranasalen Tumoren aus, und nur 20% dieser seltenen neuroektodermalen Tumoren werden bei Patienten ≤ 20 Jahre diagnostiziert. Radiotherapeutische und chirurgische Verfahren sind etablierte Behandlungsmodalitäten bei dieser Tumorentität. Allerdings ist die Rolle der Chemotherapie, insbesondere in multimodalen Therapiekonzepten, nur wenig definiert. Um den Einfluss der Radio- und Chemotherapie in der Behandlung von Kindern und jungen Erwachsenen mit Ästhesioneuroblastom zu untersuchen, wurde diese retrospektive Analyse durchgeführt.

Patienten und Methodik: 19 Patienten mit Ästhesioneuroblastom ≤ 20 Jahre (neun männlich und zehn weiblich) wurden in die Analyse eingeschlossen. 4/19 Patienten hatten einen Tumor Stadium Kadish B und 15/19 Patienten ein Stadium C. 17 Patienten waren operiert worden, entweder ohne weitere Therapie (n = 4), gefolgt von einer Radiotherapie (n = 1) oder im Rahmen multimodaler Therapieansätze (n = 12; Tabelle 3). Zwei Patienten hatten eine alleinige Radiochemotherapie erhalten. Bei 15/17 Patienten, die operiert worden waren, wurde eine komplette Resektion erzielt. Bei allen fünf Patienten, die eine neoadjuvante Chemotherapie infolge inoperabler Primärtumoren erhalten hatten, konnte eine R0-Resektion erreicht werden.

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** The following participating German institutions recruited patients in this retrospective study: Klinikum Augsburg, Universitätsklinikum Düsseldorf, Universitätsklinikum Erlangen, Universitätsklinikum Frankfurt, Universitätsklinikum Freiburg, Universitätsklinikum Gießen, Universitätsklinikum Hamburg, Universitätsklinikum Münster, Klinikum Hannover Nordstadt, Klinikum Oldenburg, Katharinenhospital Stuttgart, Olgaspital Stuttgart, Universitätsklinikum Tübingen, Universitätsklinikum Ulm, Universitätsklinikum Würzburg.

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Results: Das 5-Jahres-Gesamtüberleben (OS) aller Patienten betrug 73% ± 12%, das ereignisfreie 5-Jahres-Überleben (EFS) 55% ± 13% (Abbildung 2). Keiner der vier Patienten im Stadium B entwickelte eine Tumorprogression, wohingegen es bei sieben von 15 Patienten im Stadium C zu einer Tumorprogression kam (5-Jahres-EFS 47% ± 14%; nicht signifikant; Abbildung 3). Patienten mit Stadium C und multimodalen Therapieansätzen (Operation, Radio- und Chemotherapie) hatten einen signifikant besseren Verlauf als Patienten im Stadium C mit weniger als drei Therapiemodalitäten (65% ± 17% vs. 20% ± 18%; p = 0,02; Abbildung 4).
Schlussfolgerung: Diese Daten zeigen, dass multimodale Therapiestrategien mit Operation, Chemo- und Radiotherapie für pädiatrische Patienten mit Ästhesioneuroblastom im Stadium Kadish C einen Vorteil im Krankheitsverlauf bringen. Der Einsatz der Chemotherapie scheint die Resektabilität, das EFS und das OS zu verbessern. Die Radiotherapie ist ein integraler Bestandteil in der Behandlung von Kindern und jungen Erwachsenen mit Ästhesioneuroblastom im Stadium B und C.

Schlüsselwörter: Kindliches Ästhesioneuroblastom · Olfaktoriusneuroblastom · Radiotherapie · Multimodale Therapie · Chemotherapie

Introduction

Esthesioneuroblastoma (ENB) is a rare and uncommon neuroectodermal tumor arising from the olfactory epithelium in the upper nasal cavity and often shows an intracranial extension [5]. This tumor constitutes 3% of all intranasal neoplasms. Since the first description of ENB by Berger & Luc [1] in 1924, about 1,000 cases have been reported in the world literature [5]. ENB can occur in all ages, with peaks in the 2nd and 6th decades of life [1, 5]. Generally, ENB is relatively rare in children [4, 14, 27, 31]. The incidence in children up to 15 years is < 0.1 per 100,000 children (personal communication Dr. P. Kaatsch, German Childhood Cancer Registry, University of Mainz, Germany). Bobele et al. reported that only 20% of all ENB are diagnosed up to 20 years of age [4].

As in all intranasal tumors, initial symptoms are mostly nonspecific and include nasal obstruction, epistaxis, cephalgia, hyposmia, exophthalmos, and amaurosis in correlation to the tumor extension.

Since pediatric ENBs are rare, the number of children and adolescents treated in individual departments is very small. Almost all studies in the literature are retrospective reports, often case reports [4, 5, 8, 12, 14, 23, 31]. Randomized treatment trials are not practical for such a rare tumor. Optimal treatment is still discussed controversially. Most children are treated based on reviews of adult cases and series. Treatment has generally involved extensive craniofacial resection along with radiotherapy. Chemotherapy has been reported mainly for recurrent or metastatic disease [10–12, 25, 26, 30].

The present analysis of 19 children and adolescents with ENB was performed to evaluate the efficacy of radiotherapy and chemotherapy especially in a multimodal treatment approach in this age group.

Patients and Methods

This study comprises a retrospective multicenter review of 19 children and young adolescents (≤ 20 years) with ENB treated from January 1979 to August 2001. A questionnaire including data of the patients' characteristics, initial presenting symptoms, tumor extent, primary therapy, tumor recurrence and follow-up was sent to all treatment centers of pediatric oncology in Germany. In 2001 we initiated a prospective documentation of any ENB diagnosed in Germany in the German Neuroblastoma Study Center in Cologne, Germany. All available clinical data including histological and radiographic reports were reviewed. Diagnosis of ENB was based on histopathologic features according to common rules [15, 32] and radiologic localization of the tumor. Histology was confirmed by an expert pediatric pathologist in 16 of 19 included patients. In the histopathologic diagnosis of ENB immunohistochemistry and electron microscopy are helpful. ENB may be confused with lymphoma, extramedullary plasmocytoma, undifferentiated carcinoma, malignant melanoma, rhabdomyosarcoma and Ewing's tumor family. Especially the positive reaction for S-100 protein and the presence of neuron-specific enolase (NSE) in combination with a negative stain for epithelial and lymphoma marker suggest its classification as a neurogenic tumor [15, 32].

Patients were staged according to the Kadish system (Table 1) which is predominantly used in literature, although multiple modifications have been proposed [3, 5, 9, 16]. For reasons of comparability we have chosen the original system.

Radiotherapy was performed with linear accelerators mostly in three-field technique: an anterior field combined with wedged lateral fields. Before 1985 radiotherapy was calculated on midplane. When computed tomography treatment planning was available, the target volume (PTV) encompassed the primary tumor site and varied upon the tumor extension including a safety margin of 1–2 cm. The PTV had to be cov-

Table 1. Stages according to Kadish et al. [16].

Tabelle 1. Stadieneinteilung nach Kadish et al. [16].

Type	Extension
A	Tumor limited to the nasal cavity
B	Tumor infiltrating the nasal and paranasal cavities
C	Tumor extending beyond the nasal and paranasal cavities

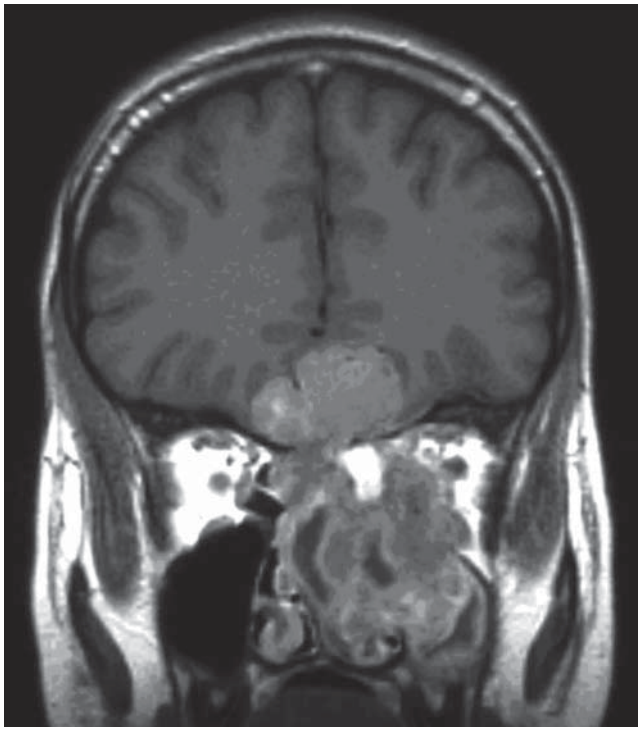

Figure 1. Esthesioneuroblastoma in Kadish stage C at diagnosis infiltrating the orbita, the nasal and paranasal cavities, and the brain.

Abbildung 1. Ästhesioneuroblastom im Stadium Kadish C mit Infiltration der Orbita, der Nasenhaupt- und -nebenhöhlen sowie des Gehirns.

ered by the 90% isodose. Patients treated in the last years were irradiated based on three-dimensional radiation treatment planning. This special planning method allows individual dose adjustment to an irregularly shaped PTV by using (micro-)multileaf collimators and noncoplanar beam arrangements. For patients with radiotherapy (n = 15), the median dose to the target volume was 50 Gy (range, 32–60 Gy), median dose per fraction 2 Gy, and median number of fractions 25 (range, 16–30).

Table 2. Presenting symptoms of esthesioneuroblastoma in 19 children and adolescents.

Tabelle 2. Initiale Symptome bei 19 Kindern und Jugendlichen mit Ästhesioneuroblastom.

Symptoms	Patients (n)
Nasal obstruction, rhinitis	9
Epistaxis	8
Exophthalmos	7
Visual dysfunction/diplopia	6
Headache, facial pain	6
Tumor mass	5
Nausea, vomiting	3
Loss of sense of smell	1
Mental change	1

Table 3. Treatment strategies in 19 children and adolescents with esthesioneuroblastoma. CT: chemotherapy; RT: radiotherapy.

Tabelle 3. Behandlungsstrategien bei 19 Kindern und Jugendlichen mit Ästhesioneuroblastom. CT: Chemotherapie; RT: Radiotherapie.

	All (n)	Stage B (n)	Stage C (n)
Surgery	4	1	3
Surgery + RT	1	1	–
RT + CT	2	–	2
Multimodal			
• Surgery + CT/RT	7	2	5
• CT + surgery + RT	5	–	5

Statistical Analysis

Treatment response was assessed by clinical examinations and since 1985 by computed tomography or magnetic resonance imaging and classified as complete response, partial response, stable disease, and progressive disease according to common rules. Kaplan-Meier estimates for overall survival (OS) and event-free survival (EFS) were calculated and compared by the log-rank test [17]. For the OS death of any cause was counted as an event. For the EFS every recurrence, progression and death were counted as events. Data were analyzed using SPSS® statistical software (Release 11.0, SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

A total of 19 patients (nine male, ten female) registered from 15 oncologic centers were included in the analysis presented here. Age at diagnosis ranged from 5 to 20 years (median 14.0 years). There were three patients between 5 to 10 years, eight patients between 11 to 15 years, and eight patients between 16 to 20 years. Tumor staging was Kadish stage B in four and stage C in 15 patients. 12/15 patients with stage C tumors showed orbital infiltration, 10/15 patients cranial base and 5/15 patients brain infiltration (Figure 1). Two patients had cervical lymph node metastases initially. No distant metastases were found in the pretherapeutic tumor staging. Clinical symptoms at the time of diagnosis are listed in Table 2.

Treatment

17 patients underwent surgery, either without further therapy (n = 4), followed by radiotherapy (n = 1) or as part of multimodal regimens (n = 12). Multimodality regimens consisted of neoadjuvant chemotherapy followed by surgery plus postoperative radiotherapy in five patients or surgery plus postoperative radiotherapy and chemotherapy in seven patients. In two patients, chemotherapy and radiotherapy scheduled prior to surgery resulted in complete regression of the primary; therefore, they underwent no radical tumor resection (Table 3).

Table 4. Chemotherapeutic agents in 14 children and adolescents with esthesioneuroblastoma.

Tabelle 4. Chemotherapeutika bei 14 Kindern und Jugendlichen mit Ästhesioneuroblastom.

Chemotherapy	Patients (n)
Vincristine/vindesine	13
Ifosfamide/cyclophosphamide	12
Doxorubicin	11
Etoposide/teniposide	8
Cisplatinum/carboplatin	8
Actinomycin D	5
Dacarbazine	6
Methotrexate, intrathecal	1

Complete resection (R0) was achieved in 15 out of 17 patients with surgery including all five patients with preoperative chemotherapy due to unresectable primary at diagnosis.

As there were no common treatment recommendations for ENB during this 21-year time span, chemotherapeutic agents were used in various combinations, mostly based on trials for childhood neuroblastoma or soft-tissue sarcoma. Table 4 gives an overview on the applied agents.

Treatment to the neck in two patients, who had palpable nodes at presentation, consisted of therapeutic lymph node dissection and postoperative radiotherapy in one patient, and neoadjuvant chemotherapy followed by therapeutic lymph node dissection and postoperative radiotherapy in the other. None of the patients without clinically involved lymph nodes received elective lymph node irradiation or neck surgery. An elective neck dissection is not standard [5].

Treatment Outcome

Median follow-up of surviving patients was 37 months (range, 3–276 months). The 5-year OS for the whole group was 73% ± 12% and the 5-year EFS 55% ± 13% (Figure 2). None of the four patients with stage B experienced tumor progression so far, whereas seven out of 15 patients with stage C did (5-year EFS 47% ± 14%, n.s.); four of those died (Figure 3). None of the patients developed distant metastases. Patients with Kadish stage C and multimodal treatment strategies combining surgery, chemotherapy and radiotherapy had a significantly better outcome than patients with stage C and less than three treatment modalities (EFS 65% ± 17% vs. 20% ± 18%, last estimation; p = 0.02; Figure 4).

Due to the limited number of patients we could not estimate the role of the different chemotherapeutic regimens used.

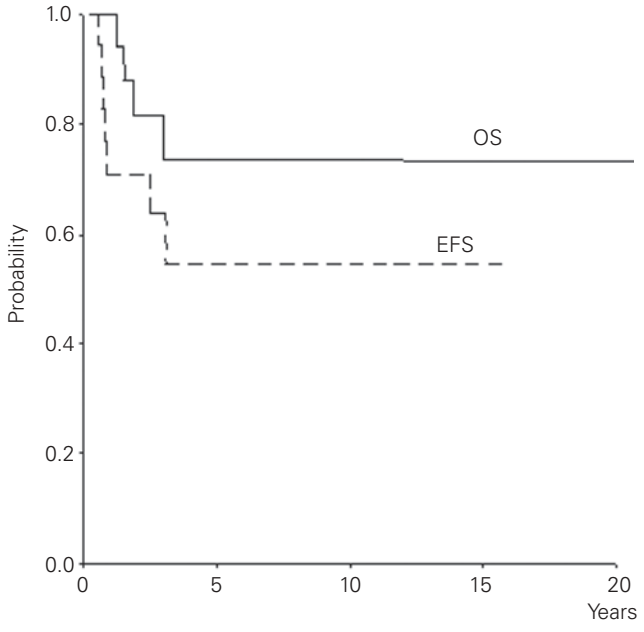

Figure 2. Overall survival (OS) and event-free survival (EFS) in 19 children and adolescents with esthesioneuroblastoma. 5-year OS 73% ± 12%; 5-year EFS 55% ± 13%.

Abbildung 2. Gesamtüberleben (OS) und ereignisfreies Überleben (EFS) von 19 Kindern und Jugendlichen mit Ästhesioneuroblastom. 5-Jahres-OS 73% ± 12%; 5-Jahres-EFS 55% ± 13%.

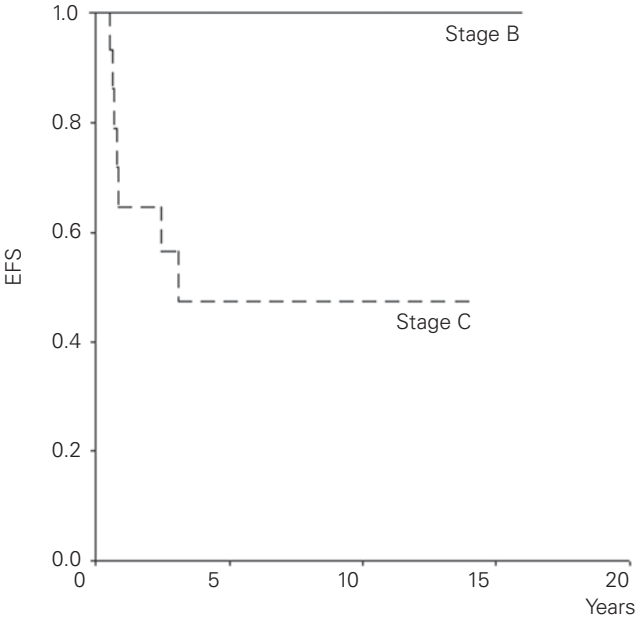

Figure 3. Event-free survival (EFS) in 19 children and adolescents with esthesioneuroblastoma by stage. None of the four patients with stage B experienced tumor progression, whereas seven out of 15 patients with stage C did (5-year EFS 47% ± 14%; not significant).

Abbildung 3. Ereignisfreies Überleben (EFS) von 19 Kindern und Jugendlichen mit Ästhesioneuroblastom, bezogen auf das Stadium. Keiner der Patienten im Stadium B entwickelte eine Tumorprogression, wohingegen es bei sieben von 15 Patienten im Stadium C zu einer Tumorprogression kam (5-Jahres-EFS 47% ± 14%; nicht signifikant).

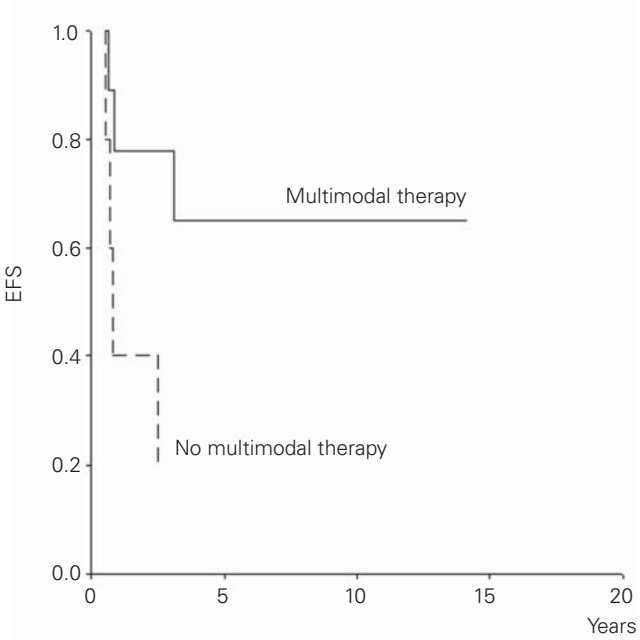

Figure 4. Event-free survival (EFS) in 15 children and adolescents with esthesioneuroblastoma stage C by initial treatment. EFS multimodal therapy (n = 10) 65% ± 17% versus no multimodal therapy (n = 5) 20% ± 18%, last estimation; p = 0.02.

Abbildung 4. Ereignisfreies Überleben (EFS) von 19 Kindern und Jugendlichen mit Ästhesioneuroblastom im Stadium Kadish C, bezogen auf die Primärtherapie. EFS bei multimodaler Therapie (n = 10) 65% ± 17% versus keine multimodale Therapie (n = 5) 20% ± 18%, letzte Berechnung; p = 0,02.

Local Recurrence

Local recurrence occurred in 7/29 patients (37%) after a median of 10 months following diagnosis (range, 7–37 months). Median survival from local relapse was 14 months (range, 5–269 months). 2/4 patients (50%) with surgery showed local relapse only. Two patients with definitive radiotherapy plus chemotherapy developed progressive disease 1 month and 2 years, respectively, after the end of initial therapy. 3/12 patients (20%) with multimodality therapy developed local recurrences.

Information on salvage therapy for the first relapse was available for all seven locally relapsing patients. For those two patients with initial surgery only, salvage therapy consisted of surgery plus radiotherapy plus chemotherapy. Both patients are still in complete remission. Two patients with initial radiotherapy plus chemotherapy received chemotherapy as salvage therapy; both died, one of them therapy-related. Three patients of the multimodality group received salvage chemotherapy; two of them died from tumor progression.

Late Toxicity of Multimodality Therapy

In patients who are still alive after multimodality therapy, late toxicity according to the WHO classification [34] could be evaluated. It was acceptable including hearing dysfunction (n = 1), amenorrhea (n = 1), slight facial asymmetry (n = 3), nasal deviation (n = 1), loss of sense of smell (n = 1), xerostomia (n = 1), retinopathy (n = 1), and cardiotoxicity WHO grade 2 (n = 1).

Discussion

The current paper presents treatment and survival data of a significant number of children and adolescents with ENB. It comprises the largest pediatric study group in the available literature.

Tumor etiopathogenesis of ENB is not yet clear. Vollrath [33] induced a tumor in the olfactory region of rats by applying nitrosamine. These tumors were morphologically and histobiochemically equivalent to ENB. Further examinations showed aberrations in chromosome 1. These chromosome aberrations were interpreted as the basis for tumor induction in this animal model [31]. Other authors discuss a viral genesis. Polyomavirus has been seen in neuroepithelial tumors of mice [6]. Mice from a transgenic line that expressed the human adenovirus type 12E1A and E1B genes tended to develop ENB at approximately 6 months of age. In most cases type C retrovirus particles were seen in the tumor rosettes [20]. In the same study three cases of feline C-particle positive ENBs were reported. Also in cats, spontaneous olfactory neuroblastomas type C retroviral particles have been seen. These particles have been classified as feline leukemia virus (FeLV) by polymerase chain reaction and immunohistochemistry. It may be interesting that these cats did not show any other evidence of neoplasms or leukemia [29].

The following findings emerge from this analysis: first, ENB is a very rare intranasal tumor, but can also be found in childhood and adolescence. Pediatricians should be aware of this tumor and should take it into account as a differential diagnosis. Second, histology should be confirmed by an expert pediatric pathologist due to the rarity of these tumors and the complexity of immunohistochemistry. Four patients were excluded from the presented study, since reference pathology showed a rhabdomyosarcoma (n = 2), a primitive neuroectodermal tumor (PNET, n = 1), and a malignant mesenchymal tumor (n = 1). Third, the presented data indicate a stage-adapted therapy and especially a benefit of multimodal treatment regimens combining surgery, chemotherapy and radiotherapy for pediatric patients with ENB Kadish stage C.

The first report about a child with ENB was published in an 11-year-old patient in 1929 and a 14-year-old patient in 1959 in the US literature [31]. A review of the world literature by Broich et al. [5] in 1997 assessed about 945 cases of ENB reported up to that time. Some of the articles included in that review do not give an age breakdown of their patients. Kumar et al. reported on five own treated children with ENB and reviewed the English literature for previously described cases of children and adolescents with ENB. Approximately 90–100 children and adolescents (≤ 20 years) have been described with this tumor in the literature, making it an extremely rare pediatric entity [23]. Furthermore, ENB has also been ob-

served to behave differently and tends to be more aggressive in the younger population [4, 16, 24].

The wide variety of treatment approaches in the current analysis, which is due to the multiinstitutional collection of ENB patients, reflects the absence of commonly accepted therapeutic recommendations. A meta-analysis of the literature published between 1990 and 2000 [8] reports an OS and a 5-year disease-free survival of 45% (standard deviation [SD] = 22) and 41% (SD = 29), respectively, in 390 patients including all ages. Survival according to treatment modalities was as follows: 65% for surgery plus radiotherapy; 51% for radiotherapy and chemotherapy; 48% for surgery; 47% for surgery, radiotherapy, and chemotherapy; and 37% for radiotherapy alone. Unfortunately, these data were not analyzed according to the stage of the disease.

Treatment of children with ENB has changed considerably over time. Most of the older pediatric literature describes primary surgical resection of the tumor followed by postoperative radiotherapy [18, 19, 22, 31]. As in adults, radiation doses of 45 Gy preoperatively and 50–60 Gy postoperatively were recommended [5, 28]. Surgery plus postoperative radiotherapy had been suggested as the standard treatment in ENB in children at that time. There is no report about the use of chemotherapy in those years. Chemotherapy for ENB was introduced in pediatric ENB between 1980 and 1990. At the same time, multicenter trials for other pediatric malignancies were established. Chemotherapy for ENB was initially reserved for patients with relapses, metastatic or inoperable disease and occasionally used in the adjuvant setting [4, 5, 23]. In the review by Bobele et al. [4] of the 26 pediatric patients described, 18 had surgery, 16 radiotherapy, and six chemotherapy. Neoadjuvant chemotherapy was reported in one patient only.

The agents most frequently used are cisplatin, etoposide, adriamycin, cyclophosphamide, vincristine, 5-fluorouracil, doxorubicin, and thiotepa. In individual cases there are data about the successful use of neoadjuvant chemotherapy followed by surgery and/or radiotherapy in patients with stage C disease [11, 13, 23]. The value of multimodality therapy in stage C patients can be supported by data in adults. Eden et al. reported results in 16 adult patients with stage A or B and 24 with stage C disease treated with radiotherapy (median dose 50 Gy) and surgery for stage A and B disease, with addition of chemotherapy (cyclophosphamide and vincristine) for stage C disease [10]. Survival rates at 5 and 10 years were 78% and 71%, respectively. Locoregional failure developed in 15 of 40 patients. Koka et al. reported on 40 adult patients with ENB who were treated with various regimens as in the analysis presented here [21]. 16 patients were treated with a variety of chemotherapeutic combinations, including adriamycin, vincristine, DTIC, cisplatin, cyclophosphamide, and cytosine arabinoside. There were five complete responders (disease regression of 75–100%) and eleven nonresponders (remission < 50%). 6/40 patients (15%) in the series of Koka et al. [21] received multimodality therapy, consisting of neoadjuvant chemotherapy plus surgery plus radiotherapy. Although primary tumor response to chemotherapy did not result in significant survival advantage in patients treated with multimodality regimen, the disease-free interval was significantly better than in those patients who did not receive chemotherapy prior to surgery. The authors recommend a multimodality treatment approach as initial therapy.

Table 5. Proposed treatment modalities for children and adolescents with esthesioneuroblastoma according to stage.

Tabelle 5. Vorschlag zur stadienadaptierten Therapie von Kindern und Jugendlichen mit Ästhesioneuroblastom.

Kadish stage	Treatment modalities
A	Surgery only
B	Surgery → radiotherapy (50–60 Gy)
C	
• Resectable	Surgery → chemotherapy (2 cycles) → radiotherapy → chemotherapy (2 cycles)
• Unresectable	Chemotherapy (4 cycles) → surgery → radiotherapy

In the presented analysis 12/19 children and adolescents (60%) received a multimodality regimen. Five patients had neoadjuvant chemotherapy plus surgery plus radiotherapy and seven patients surgery plus radiotherapy plus chemotherapy. Neoadjuvant chemotherapy seems to have a positive cytotoxic effect in non-pretreated ENB. All five patients with neoadjuvant chemotherapy had initially inoperable tumors, but in all these patients a complete tumor resection was possible after pretreatment. For Kadish stage C patients with multimodality therapy EFS was significantly improved compared to the other treatment groups, although three patients developed local recurrences and two of them died. Whether the use of new radiation treatment techniques with the option of local dose escalation and the use of intensity-modulated radiotherapy (IMRT) can lead to an improvement of local control remains to be proven [7, 35].

The presented retrospective analysis and the review of the literature support a stage-adapted therapy of ENB in children and adolescents (Table 5): in our series no patient with Kadish stage A tumor was included. According to the literature surgery only is the standard treatment. In case of incomplete surgery radiotherapy should be added. Kadish stage B tumors should be resected, followed by adjuvant radiotherapy with a total reference dose of 50–60 Gy. Careful radiation treatment planning is necessary to avoid extensive acute and late toxicity in the regions of nose, orbitae, and the frontal brain. For Kadish stage C tumors we recommend a multimodal approach: if these tumors are judged to be completely surgically resectable, initial surgery should be performed followed by two cycles of polychemotherapy, radiotherapy, and further two cycles of polychemotherapy. If these tumors are initially inoperable, we would recommend four cyles of polychemotherapy, followed by surgery and postoperative radiotherapy. The optimal chemotherapeutic agents have to be further in-

vestigated. Currently, we are recommending alternating chemotherapy cycles of the neuroblastoma protocol (N5: cisplatinum, etoposide, vindesine; N6: ifosfamide, doxorubicine, darcabazine, vincristine; for details see [2]). Regarding the rarity of this tumor entity in children and adolescents, an international collaboration seems necessary.

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BMC Cancer

RESEARCH ARTICLE Open Access

Esthesioneuroblastoma in pediatric and adolescent age. A report from the TREP project in cooperation with the Italian Neuroblastoma and Soft Tissue Sarcoma Committees

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Abstract

Background: Esthesioneuroblastoma (ENB) is a rare, aggressive tumor with no established treatment in children. We analyzed a series of pediatric ENB patients with the aim of improving our knowledge of this disease.

Methods: 9 patients (6 males; age 0.9-18 years, median 9.9) were identified by searching the AIEOP (*Italian Association of Pediatric Hematology and Oncology*) registry and the national databases of rare tumors, soft tissue sarcomas (STS) and neuroblastomas. The data on the cases included in STS treatment protocols were collected prospectively and histology was centrally reviewed; the data and histology concerning the other children were reviewed for the purpose of this analysis.

Results: All tumors occurred in the sinonasal region with bone erosion (7 patients) and intracranial (4) or intraorbital (4) extension. Three patients were in Kadish stage B, and 6 in stage C. Complete tumor resection was very difficult to achieve, but adding chemotherapy and radiotherapy enabled tumor control in 8 patients. Response to chemotherapy was evident in 5/7 evaluable cases. Radiotherapy (48.5-60 Gy) was delivered in all children but one, due to early disease progression. With a median follow-up of 13.4 years (range 9.2-22.9), 7 patients are alive in 1st and one in 2nd complete remission. All surviving patients developed treatment-related sequelae, the most frequent being endocrine dysfunctions (4 patients) and craniofacial growth impairments (4 patients).

Conclusions: Our findings confirm that ENB in children has an aggressive presentation, but multimodal therapy can cure most patients. Our results are encouraging but future strategies must optimize treatment in terms of survival and related morbidities.

Keywords: Esthesioneuroblastoma, Olfactory neuroblastoma, Rare tumors, Nasal tumors, Chemotherapy, Radiotherapy, Late effects, Endocrine disorders

Background

Esthesioneuroblastoma (ENB), or olfactory neuroblastoma, is a rare, aggressive tumor of the sinonasal region originating from olfactory neuroepithelium. Its incidence is approximately 0.4-1/1,000,000 population per year and, though it can occur at any age, its incidence peaks in the second and fifth decades of life [1,2]. No gender predilection has been reported and its etiology is unknown, but an infectious genesis has been suggested because the tumor contains viral particles [3,4].

In pediatric age, the estimated incidence of ENB is 0.1/100,000 children up to 15 years of age, but it is the most common cancer of the nasal cavity, accounting for 28% of a series of 47 cases registered in the Surveillance, Epidemiology and End Results (SEER) database from 1973 to 2002 [2,5].

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ENB in younger patients seems to have a more aggressive presentation than in adults with a larger proportion of cases with advanced disease.

Treatment decisions are based mainly on experience gained in adults, but implementing local measures such as radical surgery and high-dose radiotherapy pose specific problems in pediatric age.

A national-scale initiative called the TREP project (Tumori Rari in Età Pediatrica, *Rare Tumors in Pediatric Age*) was launched in Italy in 2000 with the aim of improving the clinical management of children with very rare cancers (defined as pediatric solid malignancies with an annual incidence < 2/million and not considered in other clinical trials) and contributing to the related basic research [6]. As part of this scheme, the present study was designed to describe the clinical characteristics, treatment and outcome of ENB patients treated at Italian pediatric oncology centers.

Methods

All patients under 18 years of age registered by AIEOP centers with a diagnosis of ENB were included in this analysis. The cases were identified by searching the AIEOP hospital-based registry (where all Italian pediatric oncology centers register the cases they diagnose), the TREP project database (from 2000 onwards), and the database managed by the Italian Working Groups on Neuroblastoma and Soft Tissue Sarcoma. Only patients diagnosed from 1980 to December 2008 were considered to allow for an adequate follow-up.

Tumors were defined according to the staging system proposed by Kadish and modified by Morita, as follows: A - tumors confined to the nasal cavity; B - tumors infiltrating the paranasal cavities; C - tumors extending beyond the nasal and paranasal cavities; D - tumors with metastases [7,8]. The disease was also staged according to the TNM system, where T1 means tumors confined to the organ or tissue of origin, and T2 lesions invade contiguous structures; T1 and T2 are further classified as A or B by tumor diameter < or > 5 cm, respectively; N1 means regional lymph node involvement; and M1 the presence of distant metastases.

There were no specific guidelines for treating ENB so children were treated on the basis of the existing literature and, for pragmatic reasons, included in the ongoing Italian protocols for rhabdomyosarcoma (RMS) (which also included soft tissue neuroectodermal tumors) or neuroblastoma (NBL).

Informed consent to the treatment and to data collection and analysis was obtained for all patients according to institutional guidelines at the time of enrolling patients in the protocols.

Response to chemotherapy was defined as follows: complete response (CR) - clinically or histologically confirmed complete disappearance of disease; partial response (PR) - at least a two-thirds reduction in tumor volume; minor response (MR) - reduction greater than one-third but less than two-thirds; no response or stable disease (SD) - less than one-third reduction in tumor volume; progressive disease (PD) - increase in tumor size or detection of new lesions.

The data on the cases included in the protocols for RMS were collected prospectively and their histology was centrally reviewed; the data and histology on the other children were reviewed for the purpose of this analysis. Response to chemotherapy was re-evaluated on the basis of radiological reports in the two cases for whom no radiological findings were available.

The long-term sequelae were only ascertained by contacting the clinical investigators at the various centers; no additional investigations were conducted on possible late effects for the purpose of this study.

Results

Overall, 11 patients with ENB were registered, but full details were only available for 9 of them (6 males; age 0.9-18 years, median 9.9). The patients' demographic data are shown in Table 1.

Symptoms were non-specific and usually involved nasal obstruction, headache and epistaxis. One child had an epileptic episode and revealed a mass in the olfactory region that extended intracranially.

In addition to computed tomography or magnetic resonance imaging, metaiodobenzylguanidine scans were obtained for 4 patients but none of them were positive. The initial diagnosis was NBL in 2 cases and PNET in 1, but was changed to ENB after central review soon afterwards. Nearly all tumors were large (> 5 cm in maximum diameter) and aggressive, with bone erosion (7 patients) and intracranial (4) or intraorbital (4) extension. Regional lymph nodes were involved in 3 children. The Kadish stage was consequently C in 6 patients and B in 3.

Treatment

The treatments administered are summarized in Table 2. At diagnosis, tumor resection was attempted in 4 cases but was always incomplete, while only a diagnostic biopsy was obtained in 4. Lymph node biopsy was performed in one case. No major postoperative complications were reported. All patients received multidrug chemotherapy: 6 were enrolled in protocols proposed for children with RMS and 3 in protocols for children with NBL. The regimens changed over time but the children on the RMS protocol mainly received chemotherapy based on the association of vincristine, doxorubicin, ifosfamide, actinomycin D (VAdIA), while those on the NBL protocol were given cycles with

Table 1 Clinical characteristics of 9 patients with esthesioneuroblastoma

Pt.	Sex/age at dgn (years)	Symptoms	Primary site	Tumor extension	Tumor size	TNM	Kadish stage
1	M/4	Seizures	Rhinopharynx	Intracranial, bone erosion, cervical lymph nodes	> 5 cm	T2b, N1, M0	C
2	M/2	Exophthalmos	Nasal cavity, rhinopharynx and ethmoid sinuses	Orbital cavity, submandibular lymph node, bone erosion	> 5 cm	T2b, N1, M0	C
3	F/16	Recurrent epistaxis	Paranasal sinuses	-	> 5 cm	T1b, N0, M0	B
4	M/10	None	Nasal cavity, rhinopharynx and maxillary sinuses	Bone erosion	< 5 cm	T2a, N0, M0	B
5	M/1	Recurrent epistaxis	Nasal cavity, ethmoid sinuses	Intracranial, bone erosion	> 5 cm	T2b, N0, M0	C
6	M/11	Nasal obstruction	Nasal cavity, maxillary and ethmoid sinuses	-	> 5 cm	T2b, N0, M0	B
7	M/5	Cranial nerve palsy	Nasal cavity pterygomandibular, infratemporal fossae	Intracranial, orbital cavity, bone erosion	> 5 cm	T2b, N0, M0	C
8	F/18	Proptosis	Nasal cavity	Intracranial, orbital cavity, retromandibular and laterocervical lymph nodes, bone erosion	> 5 cm	T2b, N1, M0	C
9	F/17	Headache	Maxillary and ethmoid sinuses	Orbital cavity, bone erosion	> 5 cm	T2b, N0, M0	C

Pt: patient; dgn: diagnosis; M: male; F: female.

Table 2 Treatment details for 9 patients with esthesioneuroblastoma

Pt.	Protocol type	Initial surgery	CT (No. of cycles)	Response to CT	Delayed surgery	RT (dose)	Outcome (years after diagnosis)	Long-term sequelae
1	RMS	Macroscopic residuals	VAdIA (9)	PR	No	No	DOD (0.7)	-
2	RMS	Biopsy	VAdIA (12)	CR	No	Yes (53 Gy)	NED (11.5)	GH deficit, hypogonadism, hypothyroidism, chronic sinusitis, hypovision and cataract, hearing loss, dental abnormalities, facial bones hypoplasia
3	RMS	Biopsy	VAdIA + Carbo/E (5)	PR	Microscopic residuals	Yes (50 Gy)	NED (13)	Palate deformity
4	RMS	Biopsy	VAdIA (12)	MR	Complete resection	Yes (60 Gy)	NED (14)	Hypothyroidism, xerostomia, oligospermia
5	RMS	Microscopic residuals	VAdIA (9)	NE	No	Yes* (42 Gy)	NED (9.2)	Chronic headache, hypothyroidism, attention-deficit/ hyperactivity disorder
6	NBL	Macroscopic residuals	VAdC + CDDP/E (6)	SD	Microscopic residuals	Yes (48 Gy)	NED (11.1)	loss of sense of smell, facial bone hypoplasia, recurrent keratoconjunctivitis, maculopathy
7	NBL	Biopsy	VAdCA + CDDP/E + i.t. MTX (15)	PR	No	Yes (60 Gy)	NED (23)	Amaurosis, hypothyroidism, GH deficiency, xerostomia, facial bones hypoplasia
8	NBL	Lymph node biopsy	VAdC/ CDDP (7)	CR	No	Yes (47 Gy)	NED (20.2)	Peripheral neuropathy
9	RMS	Macroscopic residuals	VAdC (12)	NE	No	Yes (60 Gy)	NED (17.1)	Chronic sinusitis

Pt: patient; CT: chemotherapy; RT: radiotherapy; RMS: rhabdomyosarcoma; V: vincristine, Ad:adriamycin, I: ifosfamide, A actinomycin-D; PR: partial response; DOD: dead of disease; CR: complete response; Gy: grays; NED: not evidence of disease; GH: growth hormone; Carbo: carboplatin; E: etoposide; PR: partial response; MR: minor response; NE: not evaluable; NBL: neuroblastoma; C: cyclophosphamide; CDDP: cisplatin; SD: stable disease; i.t. MTX: intrathecal methotrexate

vincristine, doxorubicin and cyclophosphamide (VAdC) alternated with the cisplatin-etoposide combination. The duration of chemotherapy varied considerably, with a total of 5 to 15 cycles being administered.

*pt No. 5 received radiotherapy after tumor relapse. Major tumor shrinkage was evident after chemotherapy in 5 of the 7 cases evaluable (2 CR and 3 PR). Response was not evaluable in 2 patients because the tumor was resected at diagnosis in one (No. 5), and because one child had already been irradiated during initial chemotherapy (No. 9). Delayed tumor resection was attempted in 3 patients and was complete in one. Radiotherapy (47-60 Gy) was delivered during the first-line treatment to all but two children: one progressed just before starting radiotherapy; the other was a very young child who was irradiated only after tumor relapse.

Outcome

With a median follow-up of 13.4 years (range 9.2-22.9), 7 patients are alive in 1st CR. The young child who was not irradiated during first-line therapy (No. 5) relapsed in the locoregional lymph nodes 20 months after completing the treatment, but achieved a 2nd long-lasting CR after tumor resection and further chemo- and radiotherapy. The disease progressed in one patient (No. 1), who died 9 months after diagnosis. The 5-year progression-free and overall survival (OS) rates were thus 77.8% (36.6%-93.9%) and 88.9% (43.3%-98.4%), respectively.

The most frequent long-term adverse effects were endocrine dysfunctions and craniofacial growth impairment (affecting 4 patients each). Other reported sequelae included ocular damage (2), xerostomia (2), chronic sinusitis (2), damage to permanent teeth (1), loss of the sense of smell (1), and behavioral disorders (1). Fertility problems and neuropathies relating to the chemotherapy administered were also reported.

Discussion

Our report confirms that ENB is very rare in pediatric age and that its behavior is aggressive, since most children presented with locally disseminated disease. As localized ENB (Kadish stage A) seems to be rare in children, and our series only contained tumors in Kadish stages B and C, our discussion focuses on locally advanced ENB.

Tumor resection is generally the first therapeutic measure in adults with ENB (though this often requires a craniofacial approach), followed by radiotherapy [9]. Chemotherapy is mainly reserved for patients with advanced, recurrent or metastatic disease. Preoperative radiotherapy in doses in the range of 55 to 65 Gy has been preferred by some authors for stage C ENB [10]. These procedures are highly aggressive, however, and skull base surgery is particularly difficult in children because of the small size of the area, and because of the bone and neurovascular structures located in the craniofacial region. Up to one in three patients therefore risk postoperative morbidities, including complications involving the local wounds, the central nervous system (e.g. cerebrospinal fluid leakage and meningitis) and the ocular orbit. Postoperative mortality has also been reported in up to 5% of patients [11]. Radiotherapy may also cause significant late effects in children, including craniofacial growth impairment and damage to the permanent teeth, endocrine dysfunctions, and loss of the sense of smell [12]. In our series, multiple-agent chemotherapy was adopted systematically and judged preferable to invasive surgery as an initial approach. This had numerous advantages for the patients, since no major surgical complications were reported and tumor shrinkage after chemotherapy meant that delayed surgery could be less aggressive. Unfortunately, complete tumor resection was still very difficult to achieve, but our experience suggests that chemotherapy and radiotherapy may be enough to control postoperative residuals, and some patients were cured without any major surgery.

In our experience radiotherapy is the mainstay of treatment for ENB, as it is for other parameningeal pediatric tumors for which surgery cannot be considered oncologically complete. Two young children in our series were not irradiated and both relapsed locally, but one of them was cured thanks to further treatment, including radiotherapy. Experiences and other data in the literature indicate that irradiation should not be withheld, but future studies should address whether a major response to initial chemotherapy might be enough to reduce the burden of irradiation and its likely long-term sequelae. New techniques, such as proton therapy, may also be helpful to limit the side effects of treatment [13,14].

Our findings show that ENB in children can be considered a chemosensitive tumor. This is in agreement with recent reports of tumor size reductions when chemotherapy was given preoperatively [12,15]. The agents most often used in children are doxorubicin, cyclophosphamide/ifosfamide, vincristine, and etoposide, whereas platinum-based regimens are adopted in adults [16].

The above drugs were used in our studies too, and gave rise to a satisfactory response rate. The limited number of children in our series made it impossible to analyze the different regimens separately or make any more precise recommendations on the type and duration of chemotherapy. This could be done by considering other experiences too, comparing and discussing our experience with those of other national groups interested in rare pediatric tumors. This is one of the main future goals of the TREP Project. In our opinion, the overall strategy for unresectable tumors may be similar

to the one adopted for other parameningeal tumors, namely RMS, for which intensive chemotherapy and early radiotherapy are recommended.

The survival results reported here are higher than those described in previously-published series. This may be due to the systematic use of a multidisciplinary approach in all the patients concerned. It may also be that ENB is more aggressive in children than in adults and/or more sensitive to current treatments. This seems to be the case for other rare tumors that behave differently in different age groups. Unfortunately, the need for an aggressive treatment approach can also mean severe side effects and this issue should be addressed when planning future treatments.

Conclusion

In conclusion, our findings confirm that ENB has aggressive features in children, but a multimodal approach - relying mainly on chemotherapy and radiotherapy - can cure most patients. This is an encouraging result, but more data are needed to optimize strategies for treating pediatric ENB in terms of patient survival and treatment-related morbidities.

The limited number of ENB patients analyzed in this collaborative effort as part of the TREP project goes to show that we need to move from national to international cooperative schemes in order to obtain more solid evidence to guide the treatment of such very rare tumors as ENB.

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Authors' contributions

GB conceived the study, coordinated the data analysis and drafted the manuscript. PS collected the data and cooperated on the data analysis and the drafting of the manuscript. GC reviewed the data on local treatments and critically revised the manuscript. MC, AF, MP, AG, RL made substantial contributions to the conception of the study and to data acquisition, as well as taking part in the final analysis and the drafting of the manuscript. All authors have read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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CLINICAL REVIEW

WILEY

Esthesioneuroblastoma with distant metastases: Systematic review & meta-analysis

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Abstract

Background: The purpose of this study was to determine the clinical outcomes and review the management strategies for metastatic esthesioneuroblastoma.

Methods: We conducted a systematic review and meta-analysis.

Results: Forty-eight studies totaling 118 patients met inclusion criteria. Chemotherapy in combination with surgery and/or radiation exhibited the best overall survival when compared to monotherapy and no treatment ($P < .001$). However, most patients (66%) received either monotherapy or no therapy. The number and location of metastases among the 3 treatment groups did not significantly differ ($P = .85$). Treatment modality remained significantly associated with overall survival on multivariable analysis ($P < .001$). Platinum-based chemotherapy was most commonly utilized but did not provide a survival benefit when compared with all other regimens ($P = .88$).

Conclusion: Distant metastases with esthesioneuroblastoma portend a poor prognosis. Chemotherapy in combination with surgery and/or radiation was associated with improved overall survival. Further research into the optimal systemic therapeutic regimen for patients with distant metastases is critical.

KEYWORDS

advanced disease, esthesioneuroblastoma, metastatic, meta-analysis, olfactory neuroblastoma

1 | INTRODUCTION

Esthesioneuroblastoma, also termed olfactory neuroblastoma, is a rare malignant neoplasm that arises from the olfactory epithelium of the cribriform plate and comprises up to 6% of all sinonasal tumors.[1,2] Esthesioneuroblastomas develop insidiously due to nonspecific symptomatology, such as epistaxis and nasal obstruction. Consequently, patients often present with locally advanced disease.[3,4] Past research established that esthesioneuroblastoma bears a tendency to metastasize to regional lymph nodes in the neck, and this feature significantly increases mortality.[5,6] However, scant data exist regarding the specific implications of distant metastatic disease beyond the cervical lymph nodes as these patients are routinely categorized alongside patients exhibiting neck metastases alone due to staging convenience (ie, Kadish stage D[7]) and overall disease rarity. Furthermore, investigation of this topic within the literature is largely confined to case reports and small case series from tertiary referral centers.

As a result of these limitations, little is known about the clinical relevance or best management practices for patients with disseminated esthesioneuroblastoma. As it is, this paucity

The currently submitted manuscript represents original research that has not been previously submitted. We performed this research with approval from the Mayo Clinic Institutional Review Board (IRB 17-003572).

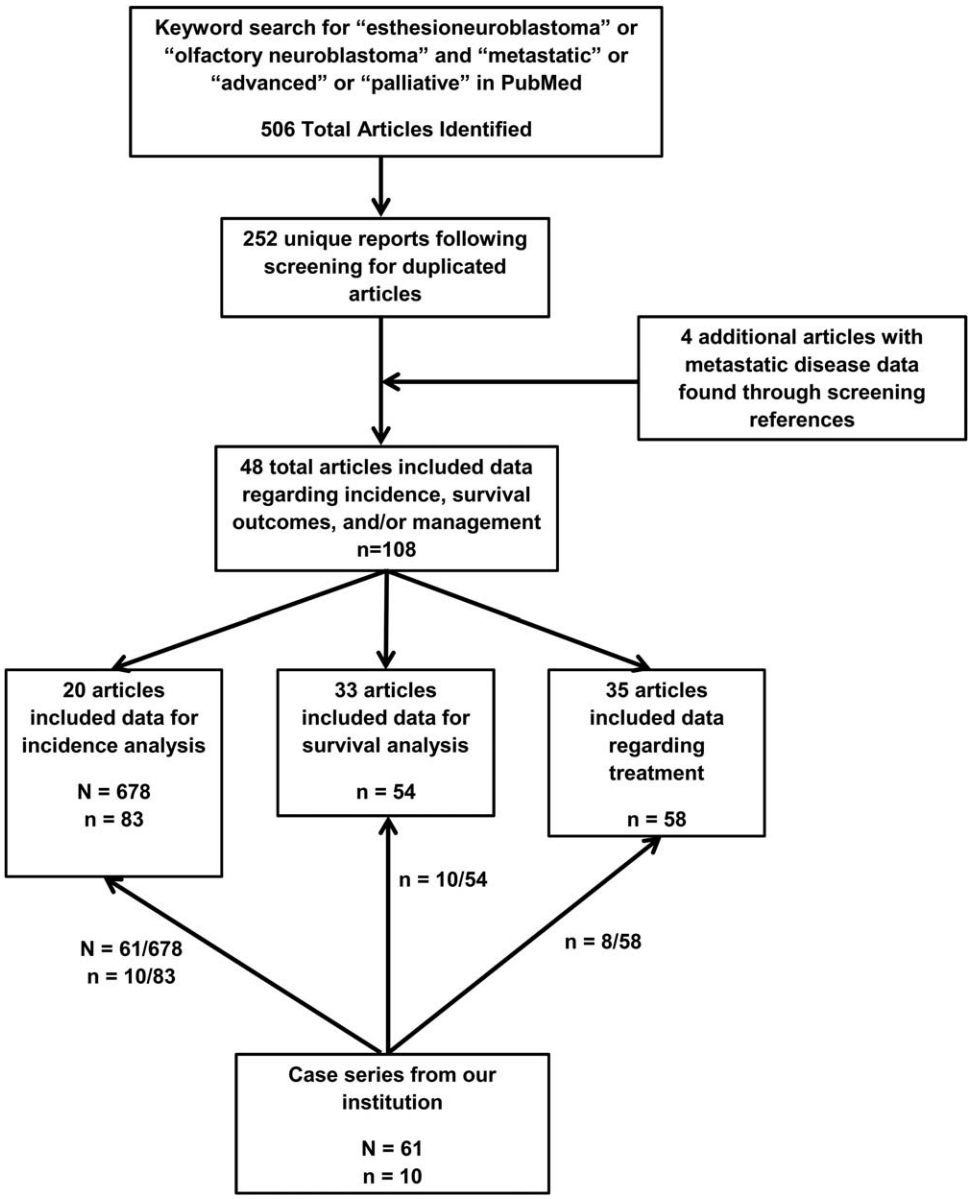

FIGURE 1 Overview of study selection and data synthesis of institutional case series (N = patients with esthesioneuroblastoma; n = patients who developed metastatic disease)

of information precludes optimal patient care. Thus, the purpose of this study was to examine the implications and current management strategies of metastatic esthesioneuroblastoma at our institution and through a systematic review and meta-analysis of the literature. The intended purpose was to present a centralized summary of the incidence, survival implications, and management strategies of esthesioneuroblastoma with distant metastatic disease.

2 | MATERIALS AND METHODS

2.1 | Metastatic disease at Mayo Clinic

After obtaining approval from the institutional review board, we conducted a retrospective review of patients who developed distant metastatic esthesioneuroblastoma from 1994 to 2016 at our institution. Distant metastatic disease was defined as disseminated disease beyond the head and cervical lymph nodes. Histological confirmation and Hyams' grading[8] in each case was made by a neuropathologist at our institution. Tumor staging at presentation used in this study was the modified Kadish staging system.[7] Synthesis of these data with the systematic review is outlined in Figure 1.

2.2 | Systematic review and meta-analysis

This systematic review and meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

guidelines.[9] Data extraction was conducted through keyword search containing "esthesioneuroblastoma" and "olfactory neuroblastoma" in conjunction with either "metastatic, advanced," or "palliative." English articles in PubMed with a publication date including or after 1995 were considered. Five hundred six articles were initially identified. After removal of duplicated search returns, a total of 252 articles were evaluated. Four additional articles were included after screening references. The complete study selection is outlined in Figure 1. Full-text manuscripts of all articles were independently reviewed unless the abstract provided definitive grounds for exclusion. We required studies to explicitly identify the location of distant metastatic disease. Cases of "intracranial" metastases were excluded due to an inability to conclusively and consistently separate such instances from locally recurrent or advanced disease. Eligible studies for analyzing the incidence of distant metastases were required to represent a complete or consecutive single or multi-institutional experience. Because this systematic review provides an amalgamation of all available evidence regarding metastatic esthesioneuroblastoma, heterogeneity among studies was assessed through descriptive analysis (eg, variation in chemotherapy regimens) in place of reporting an I^2 as is commonplace among meta-analyses. The study design of a systematic review was primarily implemented to provide a centralized and reproducible compilation of data surrounding a rare disease rather than compare study-to-study homogeneity.

2.3 | Statistical methods

Overall survival and metastases-free survival rates were estimated using the Kaplan-Meier method. Comparisons of survival among patient groups of interest were evaluated using log-rank tests. A Cox proportional hazards regression model was used to evaluate the association of age and treatment for metastatic disease with death in a multivariable setting. Associations between the location and number of metastases with the type of treatment received were analyzed using a Fisher exact test. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided and P values $< .05$ were considered statistically significant.

3 | RESULTS

3.1 | Systematic review and institutional retrospective analysis

A total of 48 unique articles met inclusion criteria for analysis of incidence, overall survival, and/or treatment (see Supporting Information Table S1 for the inclusion and exclusion criteria that each included study met).[3,10–56] Of these, 20 articles included appropriate data to calculate incidence of distant metastases. Our institutional data represented a consecutive experience and was thus included in this analysis. Thirty-three articles, totaling 44 patients, presented survival durations after the onset of distant metastatic disease. Our case series added an additional 10 patients for this analysis. Finally, 35 articles included sufficient information regarding specific treatment approaches. Fifty individual patient cases were analyzed from these studies, and our institutional data allowed for the inclusion of an additional 8 patients. In total, 118 patients with esthesioneuroblastoma who developed distant metastases were reviewed in this study, and available clinical data are presented in Table 1.

TABLE 1 Clinical data for 118 patients with esthesioneuroblastoma who developed distant metastases

Feature	No. of patients (%)
Age at diagnosis of distant metastases, years, N = 55, median (range)	51 (10-77)
Sex (N = 55)	
Female	23 (42)
Male	32 (58)
Hyams grade, N = 20	
Low	6 (30)
High	14 (70)
Primary treatment, N = 57	
Surgery	7 (12)
Surgery + radiotherapy	22 (39)
Surgery + radiotherapy + chemotherapy	10 (18)
Radiotherapy + chemotherapy	10 (18)
Other	8 (14)
Initial Kadish stage, N = 52	
A	0
B	2 (4)
C	39 (75)
D	11 (21)
Location of metastases, N = 87[a]	
Bone	35 (40)
Lung	25 (29)
Drop metastases/spine	25 (29)
Liver	10 (11)
Breast	5 (6)
Skin	3 (3)
Heart	1 (1)
Ovary	1 (1)
Intraperitoneal	1 (1)

[a]Patients with multiple metastases were included in all locations in which they had disease present.

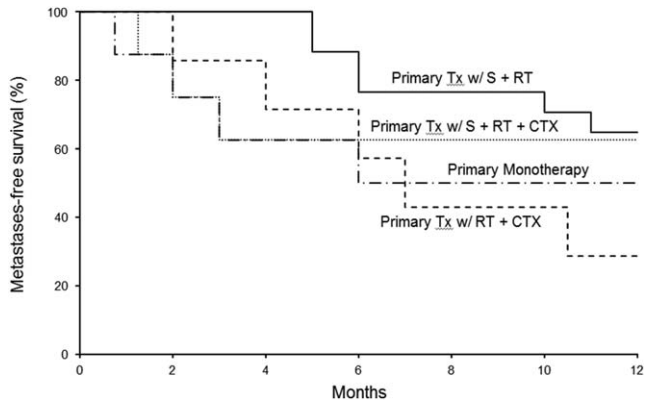

FIGURE 2 Distant metastases-free survival by treatment modality for primary esthesioneuroblastoma from the date of diagnosis. CTX, chemotherapy; RT, radiotherapy; S, surgery; Tx, treatment

3.2 | Incidence and distant metastases-free survival after esthesioneuroblastoma diagnosis

Of 678 patients pooled for incidence analysis, 83 (12%) developed distant metastatic disease. The time-to-distant metastases was reported for 40 cases, with a median time-to-distant metastases after primary esthesioneuroblastoma diagnosis of 15 months (range 0.75-276 months). The metastases-free survival rate (95% confidence interval [CI]; number still at risk) at 6 months after definitive treatment for this cohort was 65% (95% CI 52%-80%; number still at risk 30). Metastases-free survival differed significantly depending on the primary treatment modality that patients received (P = .041; Figure 2). Metastases-free survival at 6 months after primary treatment were 77% (95% CI 59%-100%; number still at risk 15) for surgery plus radiation, 63% (95% CI 37%-100%; number still at risk 5) for surgery plus radiation and chemotherapy, 57% (95% CI 30%-100%; number still at risk 5) for radiation and chemotherapy alone, and 50% (95% CI 25%-100%; number still at risk 5) for monotherapy with either surgery or radiation. Kadish C patients displayed better distant metastases-free survival compared with Kadish D patients (67%; 95% CI 52-86; number still at risk 23 vs 38%; 95% CI 15-92; number still at risk 4; at 6 months after diagnosis) but this difference did not achieve statistical significance (P = .33; Table 2).

3.3 | Overall survival and treatment

The median clinical follow-up after diagnosis of distant metastatic disease for the cohort was 9 months (interquartile range [IQR] 5-9 months; range 0.25-224 months), and only 19% of patients were still alive at last follow-up. The 6-month overall survival rate after diagnosis of distant metastases for the 54 patients with available data was 63% (95% CI 51%-77%; number still at risk 36), with drop-metastases to the spinal cord and spine exhibiting the best survival rates at 80% (95% CI 62%-100%; number still at risk 12) and visceral organ metastases (ie, lung and liver) portending the worst prognoses at 52% (95% CI 36%-76%; number still at risk 15). A third group of patients with bone metastases only exhibited a survival rate of 64% (95% CI 44%-95%; number still at risk 9) at 6 months. Most commonly, bone metastases included pelvic metastasis followed by metastases to long bones. The survival observed among these 3 groups was not statistically significantly different (P = .30; Figure 3).

Univariable analysis indicated that older patient age was associated with worse overall survival (P = .007). The median age for patients in the multimodality treatment group was 51 years (IQR 36-58 years), 38 years (IQR 24-59 years) for the monotherapy group, and 57 years (IQR 47-68 years) for the no therapy group. Kadish C patients exhibited better overall survival rates compared with Kadish D patients (66%; 95% CI 52%-84%; number still at risk 25 vs 40%; 95% CI 19%-86%; number still at risk 4 at 6 months after diagnosis of distant metastases) but this difference did not achieve statistical significance (P = .24; Table 2). Whether or not the patient developed multiple distant metastases was not significantly associated with overall survival (P = .65; Table 2). Multivariable analysis of age (P = .002) and treatment modality (P < .001) indicated that both factors independently predicted overall survival (Table 2).

Overall survival rates based on the treatment approach for metastatic disease are presented in Figure 4. Of cases that reported specific treatment approaches, 12 of 12 were no treatment cases, 18 of 26 were monotherapy cases, and 19 of

TABLE 2 Overview of all analyses performed examining factors influencing overall survival after onset of distant metastases and metastases-free survival after primary diagnosis of esthesioneuroblastoma

	Overall survival	Metastases-free survival
Univariable analysis	***P* value**	***P* value**
Age	.007[a]	.89
Kadish C vs Kadish D	.24	.33
Sex	.44	.35
Multiple metastases	.65	...
Primary treatment	...	.041[a]
Location of metastases	.30	...
S/RT + chemotherapy vs monotherapy vs no therapy	< .001[a]	...
Platinum-based chemotherapy	.88	...
Multivariable analysis		
Age	.002[a]	...
S/RT + chemotherapy vs monotherapy vs no therapy	< .001[a]	...

Abbreviations: RT, radiotherapy; S, surgery.
[a]Feature achieved statistical significance.

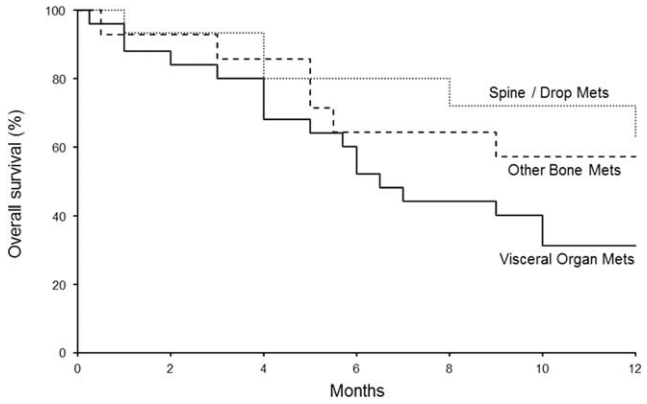

FIGURE 3 Overall survival after diagnosis of distant metastases (Mets) by location of metastatic disease

20 were multimodality treatment cases has survival data listed in Figure 4. Patients who received multimodality treatment consisting of chemotherapy in combination with surgery and/or radiation exhibited the best overall survival, whereas patients who received no therapy exhibited the poorest survival outcomes. The difference in overall survival among these 3 groups was statistically significant ($P < .001$). This feature was still significant after adjusting for age in a multivariable setting ($P < .001$; Table 2). At 6 months after diagnosis of metastatic disease, survival rates were 33% (95% CI 15%-74%; number still at risk 4) for patients who received no treatment, 56% (95% CI 37%-84%; number still at risk 11) for patients who underwent monotherapy with either chemotherapy or radiation alone, and 95% (95% CI 85%-100%; number still at risk 18) for patients who received multimodality treatment. The 2-year survival for patients receiving multimodality treatment was 63% (95% CI 43%-92%; number still at risk 7). Noting that the location of distant metastases was associated with different prognoses and given the likelihood that the number of metastases could reasonably influence survival or treatment decisions, we presented these data in correspondence with the number of patients for each treatment group in Table 3. The difference in the number of patients and the locations of distant metastases among the different treatment groups was not statistically significant ($P = .85$). Last, 66% of studies implemented platinum-based chemotherapy, with 37% of patients also receiving etoposide as combination therapy. A total of 21 different chemotherapy regimens were used across all studies. The use of platinum-based chemotherapy was not significantly associated with overall survival ($P = .88$).

4 | DISCUSSION

This study presents a systematic review and meta-analysis of esthesioneuroblastoma with metastatic disease. In a rare disease, such as esthesioneuroblastoma, it is difficult to obtain epidemiologic measures and high-quality evidence to determine efficacy of a treatment modality or strategy to help improve care for patients. Analyzing clinical and treatment characteristics in a subset of patients with esthesioneuroblastoma with distant metastasis presents these very obstacles, making systematic review the most feasible approach to answer critical questions. Therefore, we envisioned this study specifically to determine the rate of distant metastasis, survival implications, and, if possible, determine a preferable strategy or therapeutic regimen to treat systemic disease.

Our study provides the best estimate-to-date of the incidence of distant metastases in patients treated with curative-intent therapy for esthesioneuroblastoma. The most common location of distant metastatic disease was the bones (40%), drop spinal metastases (29%), and lungs (29%). This study found that distant metastases with esthesioneuroblastoma are uncommon, which points to the effectiveness of the primary treatment and propensity for local recurrence rather than distant metastasis.[57,58]

Perhaps the most clinically relevant finding was that patients who underwent multimodality treatment consisting of chemotherapy in combination with surgery and/or radiation exhibited significantly improved survival in the metastatic setting when compared with patients who received monotherapy or no therapy. Although previous speculation surrounded the utility of a multimodality treatment approach, our pooled analysis provides evidence to its superiority. This finding is potentially confounded by the lack of randomization, retrospective nature of the study, patient selection bias, and varying treatment protocols. However, this evidence is strengthened by the observation that the location and number of metastases was not significantly different for each treatment group. In addition, multimodality treatment was significantly associated with improved survival in both single variable and multivariable analysis with patient age. Therefore, the fact that the majority of patients reviewed in this study received no treatment or exclusively radiation or

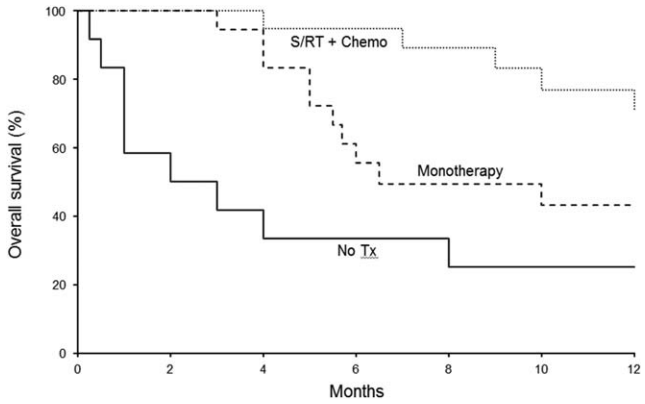

FIGURE 4 Overall survival after diagnosis of distant metastases by treatment approach for metastatic disease. CTX, chemotherapy; RT, radiotherapy; S, surgery; Tx, treatment

TABLE 3 Location and number of metastatic cases for each treatment approach

	Isolated spine	Isolated bone	Isolated organ	Multiple
No treatment (N = 12)	2	3	2 Li, 1 Lu, 1 O	3
Chemotherapy monotherapy (N = 18)	4	6	2 Li, 3 Lu	3
Radiation monotherapy (N = 8)	4	2	1 Lu	1
Chemotherapy + surgery and/or radiotherapy (N = 20)	6	5	3 Lu	6[a]

Abbreviations: Li, liver; Lu, lung; O, other.
[a]Two of these cases displayed multiple metastases to the liver and lungs.

chemotherapy emphasizes the importance of these findings for future patient care until more definitive evidence is obtained.

Successful surgical excision was demonstrated in cases of isolated lung metastases, and radiation was consistently successful as combination therapy for spinal and peripheral bone metastases. Drop-metastases to the spinal cord and spine displayed the best overall survival, whereas metastases to visceral organs portended the worst prognosis. Despite peripheral bone metastases and drop spinal metastases being consistently amendable to palliative radiotherapy, the majority of patients who received monotherapy for metastatic disease to these sites were actually treated with chemotherapy alone. This finding constitutes an area for improvement for future management of similar patients. Metastatic disease to organs, such as the liver, was often treated with chemotherapy alone, as well. Future research into stereotactic body radiotherapy should be considered for such instances. In any event, optimal management of these patients requires involvement by multiple specialties and disciplines whenever feasible.

Exploring the efficacy of specific systemic therapies, this study examined the survival impact of different chemotherapy regimens. As is commonly seen in the treatment of rare malignancies, the implemented regimens varied considerably across studies. Stemming from this treatment variation, we could not hypothesize that a unique treatment regimen was associated with improved survival and were instead forced to group them as platinum and non-platinum-containing regimens. Nevertheless, despite the esthesioneuroblastoma neuroectodermal origins,[59] platinum-based chemotherapy seemed to provide indistinguishable benefit compared with non-platinum regimens. However, these data are confounded by several factors; most notably, the multimodality treatment group and the monotherapy group had to be analyzed together due to insufficient numbers to analyze platinum versus non-platinum exclusively within the multimodality treatment group, despite the significant difference in survival highlighted in Figure 4. It is evident that further research into the optimal chemotherapy regimens for these patients is a necessity. The degree of patient care variation underscores the importance of multi-institutional participation in prospective single arm or randomized investigation into the best medical management of these patients. Investigation considerations should include targeted therapies, such as sunitinib or cetuximab, as durable responses were demonstrated in recent case studies and there is growing evidence surrounding the genomic profile of refractory esthesioneuroblastoma.[60–62]

Analysis performed in this study also substantiated previous research on primary treatment of esthesioneuroblastoma. Several studies found that surgery plus radiation improves overall survival when compared to monotherapy.[5,63] This study found that the distant metastases-free survival significantly differed depending on primary treatment, with surgery plus radiation (with or without chemotherapy) yielding the highest metastases-free survival. This finding contributes to the understanding of why patients with esthesioneuroblastoma who receive primary combination therapy exhibit improved overall survival.

Last, this review has several limitations. First, the overall incidence of distant metastases may be overestimated as many of the studies with higher populations-at-risk were reports from tertiary referral centers that likely treat a cohort of patients with more advanced disease and undoubtedly exhibit a referral bias. Therefore, these studies may have inadvertently skewed the analysis toward patients with inherently greater probability of developing distant metastases from the outset. At the same time, because distant metastases can develop over 10 years after disease onset, study variables and limited follow-up times may underestimate true incidence. As such, these 2 opposing factors may mitigate overall bias. Another limitation of this study stems from the fact that all included studies were case reports and observational studies. In this way, various provider biases may exist regarding the selection of patients that received chemotherapy for metastatic disease. We attempted to control for available factors, such as patient age and location of metastatic disease, however, other relevant clinic data, such as medical comorbidities and patient performance status, could not be taken into account, which could confound the conclusions

surrounding multimodality treatment. Unfortunately, the rarity of esthesioneuroblastoma has historically prohibited the development of higher quality, randomized prospective studies. Until such studies are conducted, this pooled analysis represents the best available evidence surrounding disseminated esthesioneuroblastoma.

5 | CONCLUSION

We show that 12% of patients treated for esthesioneuroblastoma develop distant metastatic disease, and this portends a poor prognosis. Given that distant metastatic disease can develop more than a decade after initial treatment, patients with esthesioneuroblastoma require long-term oncologic surveillance. Combination therapy comprised of chemotherapy plus surgery for oligometastatic disease and/or palliative radiation was associated with improved overall survival in the metastatic setting. Further research into systemic therapeutic regimens for these patients is critical. The degree of patient care variation underscores the importance of multi-institutional participation in prospective single arm or randomized investigation into the best medical management for these patients.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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Agosto2018 – ESTESIONEUROBLASTOMA con MTS ÓSEAS.

1.- DESCRIPCIÓN DEL CASO

Paciente de 6 años, en RMN: Tumoración centrada en celdillas etmoidales con extensión intracraneal, intraorbitaria izquierda, al seno maxilar izquierdo, ocupa la fosa nasal e infiltra clivus. Se acompaña de adenopatías metastásicas parafaríngeas bilaterales, yugulocarotídeas y cervicales posteriores bilaterales. Estos hallazgos son sugestivos de tumoración maligna tipo rabdomiosarcoma, aunque sin poder descartar otras etiologías como un estesioneuroblastoma o linfoma, valorar con biopsia.

Se realiza biopsia del ganglio y de la masa tumoral que se envian a centro de referencia y la AP es de Estesioneuroblastoma.

PET-TC: Hipermetabolismo patológico en la masa descrita sugestiva de lesión tumoral maligna de alto grado. Adenopatías hipermetabólicas laterocervicales bilaterales de características infiltrativas tumorales. Captación patológica de 18F-FDG en huesos sugestivo de metástasis óseas a distancia.

Comenzó tratamiento con quimioterapia Carboplatino 200mg/m2/día + VP-16 150mg/m2 día x 3 días, tras consulta con el coordinador nacional de tumores raros. Al finalizar en el PET-TC de control remisión completa.

(Jose Luis Perez Aguilar. Hospital Universitario de Canarias).

2.- DUDA CONSULTADA

- Dosis y Volúmenes de tratamiento.

3.- RESPUESTAS

- Jose Luis plantea la posibilidad de radiar masa + adenopatías cervicales bilaterales como tratamiento de consolidación, ya que ha habido buena respuesta al tto quimioterápico y seguimiento estricto por si apareciera cualquier metástasis óseas nuevamente y entonces valorar tratamiento. Dosis aproximada de 50 Gy.

- Después de mirar la bibliografía que adjuntas, estoy de acuerdo con tu propuesta de tratamiento y dosis. Cuantas M1 Oseas presentaba? (Sonia García).

- El PET-TC informaba: h. iliaco izquierdo (SUV max: 2.98), hemicuerpo derecho de S1 (SUV max: 3.98), hemicuerpo izquierdo L3 (SUV max: 4.27), pedículo izquierdo D12 (SUV max: 3.48), hemicuerpo derecho de D10 (SUV max: 4.89), D4 (SUV max: 3.68), D3 (SUV max: 2.95), 6º arco costal posterior derecho (SUV max: 1.95), acromio derecho (SUV max: 3.90), cuello femoral derecho (SUV max: 2.87), y en metáfisis humeral izquierda (SUV max: 2.91).

- Creo que la propuesta de consolidación con RT en la zona de tumor inicial y áreas ganglionares es una buena opción (siguiendo el patrón de otros tumores metastásicos que responden a QT) (Marta LLoret)

- Es un caso complejo y al haber respondido tan excelentemente tienta el tratar radicalmente, y coincido con lo que recomendáis de 50 Gy (quizás valorar 54 puesto que no ha habido cirugía, si la dosimetría te lo permite en zonas de tumor primitivo y 50 en zonas profilácticas del cuello si te lo planteas). El problema es las zonas metastásicas teniendo en cuenta que son múltiples y extensas , dándole mucha morbilidad su tratamiento, que siempre será paliativo. Solo me plantearía dar RT en las mts óseas que supongan un peligro inminente de fractura o compresión medular, etc... (Ismael Herruzo)

4.- CONCLUSIÓN

- Se recomienda RT área de masa primaria y ganglionar (50-54 Gy a valorar según posibilidades dosimétricas). RT en mts óseas sólo en el caso de alto riesgo de complicación.

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