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ORIGINAL ARTICLE

Importance of neoadjuvant chemotherapy in olfactory neuroblastoma treatment: Series report and literature review☆

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KEYWORDS
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Abstract
Introduction and objectives: Olfactory neuroblastoma (ONB) is a rare entity that constitutes less than 5% of nasosinusal malignancies. Mainstream treatment consists in surgical resection +/— adjuvant radiotherapy. By exposing results observed with apparition of new therapeutic options as neoadjuvant chemotherapy, the objective is to evaluate a series and a review of the current literature.
Methods: A retrospective review was conducted including patients diagnosed and followed-up for ONB from 2008 to 2015 in our institution.
Results: 9 patients were included. Mean follow-up of 52.5 months (range 10–107). Kadish stage: A, 1 patient (11.1%) treated with endoscopic surgery; B, 2 patients (22.2%) treated with endoscopic surgery (one of them received adjuvant radiotherapy); C, 6 patients (66.7%), 4 patients presented intracranial extension and were treated with neoadjuvant chemotherapy followed by surgery and radiotherapy. The other 2 patients presented isolated orbital extension, treated with radical surgery (endoscopic or craniofacial resection) plus radiotherapy. The 5-year disease free and overall survival observed was 88.9%.
Conclusion: Neoadjuvant chemotherapy could be an effective treatment for tumor reduction, improving surgical resection and reducing its complications.

☆ The authors certify that they have no affiliations or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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PALABRAS CLAVE
Estesioneuroblastoma;
Neuroblastoma olfatorio;
Quimioterapia neoadyuvante;
Resección endoscópica;
Radioterapia adyuvante

Importancia de la quimioterapia neoadyuvante en el tratamiento del neuroblastoma olfatorio: serie de casos y revisión de la literatura

Resumen
Introducción y objetivos: Elneuroblastoma olfatorio es una entidad rara que se corresponde con menos del 5% de las neoplasias nasosinusales. El tratamiento principal consiste en la resección quirúrgica ± radioterapia adyuvante. El objetivo es evaluar la sobrevida en una serie de casos y la literatura actual, mostrando resultados observados con la aparición de nuevas opciones terapéuticas como la quimioterapia neoadyuvante.
Métodos: Se realizó un estudio retrospectivo incluyendo pacientes tratados y seguidos en nuestro centro desde 2008 a 2015.
Resultados: Dentro del estudio fueron incluidos 9 pacientes. El seguimiento medio fue de 52,5 meses (rango 10-107). Estadio Kadish: A) un paciente (11,1%) fue tratado con resección endoscópica; B) 2 pacientes (22,2%) tratados con resección endoscópica (uno de ellos recibió radioterapia adyuvante); C) 6 pacientes (66,7%), de los cuales 4 presentaron extensión intracraneal y fueron tratados con quimioterapia neoadyuvante, cirugía y radioterapia adyuvante. Los otros 2 pacientes presentaron invasión intraorbitaria aislada, tratados con cirugía radical y radioterapia adyuvante. La sobrevida y periodo libre de enfermedad a 5 años fue del 88,9%.
Conclusión: La quimioterapia neoadyuvante puede ser un tratamiento efectivo para la reducción del tamaño tumoral, mejorando la resección quirúrgica y reduciendo sus complicaciones.

Introduction

ONB, also known as Esthesioneuroblastoma is a rare entity of malignant neoplasm which is believed to be formed at the neuroepithelial cells of the olfactory tract. It constitutes less than 5% of all malignant tumors of the nasal fossa and paranasal sinuses.[1] Mean age of presentation oscillates between 40 and 70 years old and has no gender predisposition.[2] The most common clinical manifestation described is nasal obstruction secondary to the presence of a mass in the nasal cavity, but it can debut with episodes of epistaxis, rhinorrhea and/or facial pain or facial fullness. Clinical examination usually demonstrates a polypoid mass located in the cranial portion of the nasal cavity. Depending on the extension and location of the tumor, different symptomatology can be observed: anosmia if it affects the cribriform plate; if it has orbital extension, can produce ocular pain, diplopia or epiphora; otalgia or otitis media with effusion if it extends to the eustachian tube; cognitive/behavioral changes with headaches if it extends to the anterior cranial fossa.[3–6] Paraneoplastic syndromes are rarely described.[7]

The diagnostic procedure requires a positive biopsy and the most commonly used staging classification is the Kadish clinical system[8] (Table 1), TNM known as Dulguerov staging system has also been described (Table 2). Hyams histological grading system grades ONB in four groups, from I to IV depending on mitotic activity and necrosis, being I/II as low grade tumors and III/IV as high grade tumors.

ONB are slow-growing tumors with unspecific symptomatology leading to a delayed diagnosis. At the moment of diagnosis most of the cases correspond to Kadish B or C stages.[2] Imaging with MRI and CT scan are essential for staging and extension. While CT gives better information about bone invasion, MRI defines more accurately margins and adjacent soft tissue extension, such as the anterior cranial fossa and orbital tissues.[9–11] PET/CT scan has importance in assessing extension in locally advanced Kadish C or Hyams III/IV cases, which have high risk of distant metastases.[12,13] Imaging studies do not differentiate ONB from other nasosinusal neoplasms.

Differential diagnosis must include neuroendocrines carcinomas, sinonasal undifferentiated carcinoma, rhabdomyosarcoma, melanomas and metastases.

To this day, due to the low frequency of this entity, treatment has not been established by randomized clinical trials and has been only assessed by retrospective observational studies.[14] Historically, management of the primary tumor has been surgery with or without adjuvant radiotherapy (ART) and in selective cases, also adjuvant chemotherapy (ACT).[15] It has been generally indicated in observational studies that overall survival (OS) and disease free survival

Table 1 Kadish staging system.

Stage	Extension
A	Confined to the nasal cavity
B	Involvement of one or more paranasal sinuses
C	Extension beyond the nasal cavity and paranasal sinuses involving cribriform lamina, skull base, orbit or intracranial cavity
D	Regional lymph node or distant metastasis

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Table 2 Dulguerov staging system.

Stage	Extension
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 cribiform plate
T3	Tumor extending into the orbit or protruding into the anterior cranial fossa
T4	Tumor involving the brain
N0	No cervical lymph node involvement
N1	Cervical lymph node metastasis present
M0	No distant metastases
M1	Distant metastases present

(DFS) are increased when treated with surgery and RT compared to RT alone.[16]

Related to surgical treatment, two different surgical approaches have been used. Endoscopic approach has the advantage of minimizing complications.[17–20] Surgical management of ONB is continuously evolving, with contemporary endoscopic approaches complementing or in many cases replacing open approaches. Aggressive, combined modality therapy appears to be justified in patients at greatest risk of developing recurrence based on advanced tumor stage and high pathologic grade. ONB requires prolonged surveillance following treatment given its tendency for late recurrence.[21,22]

The role of neoadjuvant chemotherapy (NACT) or posterior adjuvant chemotherapy (ACT) remains unclear. Many studies have tried many different chemotherapy protocols to improve survival rates without any clear results.[23–27] In palliative series a positive response to platinum and etoposide regimens have been reported.[5,28–31] Recently there are studies that report approximately 80% of tumoral response in locally advanced (Kadish C) cases with NACT, administrating 2 cycles of platinum and etoposide, which allows better surgical control and increases OS and DFS.[32]

Prognosis of ONB has been reported from an analysis of 311 cases between 1973 and 2010 in the Surveillance, Epidemiology and End Results (SEER), with a Hyams I/II and III/IV correlation, having a 10-year survival rate of 67% and 34% respectively.[2] Recently, shorter but more actual series have reported 5 and 10-year survival rates ranging from 70 to 90%.[32–36]

Materials and methods

Patient data

All patients treated for ONB at our center between the years 2008 and 2015 were included in this study. Nine patients were identified within this time interval, and their clinical records were accessed for review. Kadish system was used for staging. Every patient had a preoperative CT scan, MRI and in Kadish C patients, also a PET/CT scan was performed.

All patients were treated with curative intention. Depending on each case, management of the primary tumor consisted in surgery-alone, surgery with ART or NACT followed by surgery with ART. Mean follow-up was 52.5 months (range 10–107 months).

Treatment protocol

In all 9 cases, curative intended surgery was performed. Additional treatment with NACT or ART were added depending on the case according to the Kadish staging system. Intracranial extension included dural involvement with or without brain invasion.

Chemotherapy: NACT in cases of Kadish C with intracranial extension was a baseline of a 3-cycled cisplatin (20 mg/m^2), etoposide (75 mg/m^2) and ifosfamide (1000 mg/m^2) regimen was applied before surgery and treatment response was evaluated with an MRI 4 weeks after last dose.

Patients affected with intracranial extension, treatment with NACT followed by radical surgery and ART was applied. Kadish C patients with isolated orbital extension were treated with radical surgery followed by ART. No Kadish D stage patients were reported.

Surgery: For Kadish A and B, endoscopic surgical approach was performed adding ART in cases of affected resection margins.

For Kadish C cases with isolated orbital extension endoscopic and lateral rhinotomy approach was performed. In Kadish C cases with isolated intracranial extension an endoscopic plus bifrontal craniotomy approach was elected. The only case of Kadish C with intracranial and orbital extension was approached with both lateral rhinotomy and bifrontal craniotomy.

Radiotherapy: ART was administered in all cases as intensity-modulated radiotherapy (IMRT) with a total dose between 60 and 66 grays (Gy), given in 2 Gy per dose divided in 30–33 doses.

Statistical analysis

Estimations of OS and disease free survival DFS after curative intended treatment were performed. DFS was defined as the period of time after surgical resection that the patient survives without any signs or symptoms of ONB, while OS correspond to the length of time from surgical resection to death of any cause. For calculating DFS and OS a Kaplan–Meier method was performed using MedCalc Pro statistical analysis program.

Results

A total of 9 patients diagnosed with ONB were treated with curative intention in our institution between 2008 and 2015. Surgeries were performed by the same surgeons, 3 ORL-HNS and 1 neurosurgeon.

Average age at diagnosis was 55 years old (range 28–79), 5 male and 4 females. Mean follow-up was 52.5 months (range 10–107).

One patient (11%) was staged as Kadish A; 2 (22%) as Kadish B; 6 (67%) as Kadish C; and no patient (0%) as Kadish D (Table 3). Importance on differentiate Kadish C stage with

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Table 3 Hyams grade.

Stage	*N*	Hyams	
Kadish		Low grade (I-II)	High grade (III–IV)
A	1 (11%)	1 (100%)	0 (0%)
B	2 (22%)	2 (100%)	0 (0%)
C	6 (67%)		
-Intracranial extension	4 (44%)	1 (25%)	3 (75%)
-Orbital extension	3 (33%)	1 (33%)	2 (67%)
D	0 (0%)	0 (0%)	0 (0%)

Table 4 Patient results.

Kadish	Hyams	Extension	NACT	Surgery	Approach	ART	Follow-up (months)	Status
A	II	–	No	Yes	Endoscopic	No	107	Alive and DF
B	II	–	No	Yes	Endoscopic	No	76	Alive and DF
B	II	–	No	Yes	Endoscopic	Yes	42	Alive and DF
C	IV	Orbit	No	Yes	Endoscopic	Yes	41	Alive and DF
C	I	Orbit	No	Yes	Mixed	Yes	21	Alive and DF
C	III	IC	Yes	Yes	Mixed	Yes	85	Alive and DF
C	IV	IC	Yes	Yes	Mixed	Yes	39	Alive and DF
C	II	IC	Yes	Yes	Mixed	Yes	10	Alive and DF
C	III	Orbit and IC	Yes	Yes	Craniofacial	Yes	40	Dead of disease

DF: disease free. NACT: neoadjuvant chemotherapy. ART: adjuvant radiotherapy.

or without intracranial extension has been reported. 4 of 6 patients (67%) had intracranial extension at the moment of diagnosis.

Hyams grade was used for histological grading, 5 patients (56%) were classified as low-grade tumors and 4 (44%) were assessed as high-grade tumors.

Three different treatment modalities were reported during this study. Surgery alone was performed in 2 patients (22%), surgery with ART in 3 patients (33%) and NACT followed by surgery and ART in 4 of them (44%).

Clinical and image based follow up was performed in every patient on this series, with a mean of 52.5 months (range 10–107 months). Initial treatment was defined by Kadish stage, being endoscopic surgery in Kadish A–B cases followed by ART depending on margin affection. The Kadish A case (100%) was treated with endoscopic surgery. Kadish B cases were both treated with endoscopic surgery, and 1 (50%) required ART. Patients who had intracranial extension primary treatment consisted in NACT followed by surgery and ART. On these cases surgical endoscopic and craniofacial approach were performed in 3 cases and craniofacial approach in 1 case. From the 6 Kadish C patients, 4 (67%) had intracranial extension and 2 (33%) presented isolated orbital extension, 1 case was resected endoscopically and the other endoscopic plus lateral rhinotomy approach was necessary. Both cases received ART (Table 4).

To estimate overall (OS) and disease free survival (DFS), Kaplan–Meier survival analysis was performed. Of the 9 patients, 1 (11.1%) died from the disease at 40 months of follow-up, the other 8 (88.9%) were still alive and disease free at the end of follow-up. Mean DFS of this series was 95 months (standard error [SE] = 11.209; 95% confidence interval [CI]: 73.142–117.081) with a 5 and 10-year DFS of 88.9% (Fig. 1). Mean OS of the same series was 96 months (standard error [SE] = 10.194; 95% confidence interval [CI]: 75.854–115.813), with a 5 and 10-year OS of 88.9% (Fig. 2). No recurrence has been observed during follow up.

Discussion

The optimal treatment modality of ONB is still controversial due to limited series of cases and many treatment incongruences between publications in the current literature. The objective of this study expose a case series in

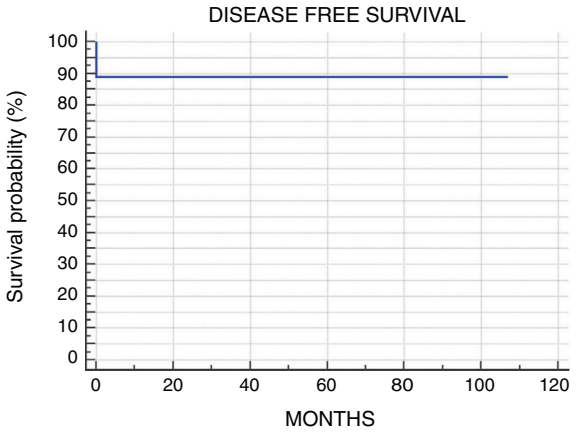

Figure 1 Disease free survival.

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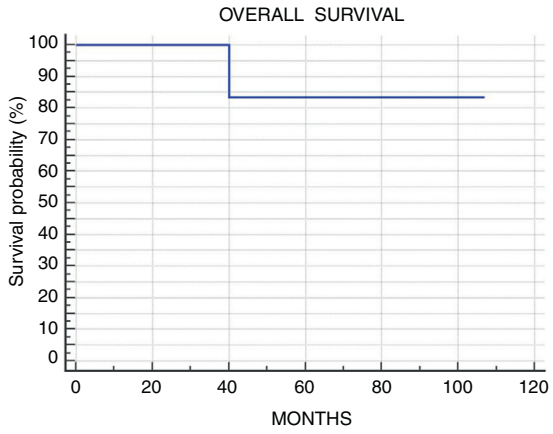

Figure 2 Overall survival.

order to add more evidence to the current literature for future reviews.

Recent series highlight the importance of endoscopic approach, that anterior skull base tumors are in reach to be controlled with correct oncological margins with endoscopic resection.[37] In a meta-analysis, comparing 49 studies with 361 cases of ONB between 1992 and 2008, greater survival rates were demonstrated with endoscopic resection than with open surgery.[38] Surgical management of ONB is continuously evolving, with contemporary endoscopic approaches complementing or in many cases replacing open approaches. Aggressive, combined modality therapy appears to be justified in patients at greatest risk of developing recurrence based on advanced tumor stage and high pathologic grade. ONB requires prolonged surveillance following treatment given its tendency for late recurrence.[21,22]

NACT has been reported to have positive response in locally advanced ONB patients. Recent studies propose cisplatin-based treatment in combination with etoposide in a 2–4 cycled CT regimen to be the protocol with best results.

Fitzek et al. in 2002 used a cisplatin (33 mg/m^2) and etoposide (100 mg/m^2) regimen for 2 cycles in Kadish B and C cases as neoadjuvant therapy, obtaining a post radical primary tumor resection 5-year DFS and OS of 88% and 74% respectively.[23]

Kim et al. in 2004 tried NACT in 11 patients with ONB, regimen consisted in cisplatin (20 mg/m^2), etoposide (75 mg/m^2) and ifosfamide (1000 mg/m^2) for a median of 4 cycles. Achieving a tumor reduction (>50%) response rate of 82%.[30]

Furthermore, Patil et al. have also used a NACT regimen with cisplatin (33 mg/m^2) and etoposide (100 mg/m^2) for a total of 2 cycles. The tumor reduction (>50%) response rate observed was 80%. After radical treatment of the primary tumor, a 5-year DFS and OS of 75% and 78.5% were obtained.[32]

Patients with intracranial extension were treated with NACT on this series. A baseline of a 3-cycled cisplatin (20 mg/m^2), etoposide (75 mg/m^2) and ifosfamide (1000 mg/m^2) regimen was applied obtaining a tumor reduction (>50%) response rate of 75%. A 5-year DFS and OS of 88.9% were achieved.

An actual retrospective studies review indicates that in locally advanced ONB cases, particularly in those with intracranial extension, NACT followed by radical treatment of the primary tumor seem to improve the 5-year DFS and OS.

Multidisciplinary management of this entity seems to be necessary. Surgery is still the main line of treatment, and minimally invasive endoscopic resection appears to be the preferred choice over more invasive approaches.

It has been seen that surgery and ART increases OS and DFS in relation to surgery or RT alone,[16] specially in locally advanced or in cases with affected resection margins.

On the current literature, multiple retrospective studies affirm that NACT could be an important line of treatment in tumors which resection is difficult such as locally advanced cases with intracranial extension.

Priority was given to endoscopic surgery versus mixed or craniofacial approach if a complete endoscopic resection could be achievable. ART was reserved for Kadish A or B cases with affected resection margins and for every Kadish C case. NACT was indicated in selected locally advanced cases with intracranial extension for the difficulty of the resection that overcomes with it.

Like most of ONB series reported in the literature, this is also a retrospective observational study and it has their own intrinsic limitations. We agree that more studies with better level of evidence are needed.

Conclusion

In the actual days NACT has been an improvement for OS a DFS in ONB series since it has been systematically used in large locally advanced tumors. There are no randomized trials or high level evidence due to its infrequency and the vast majority of the studies are retrospective studies with limited amount of patients.

It has been seen that NACT is an effective therapy for tumor reduction in olfactory neuroblastomas, allowing surgeons to achieve better surgical resection margins and reducing its complications. An increase of OS and DFS between 70 and 90% was observed in the latest series.

Complete endoscopic resection can be achieved in Kadish A, B and resecable Kadish C tumors. Although open approaches might be necessary for complete resection in more extensive neoplasms. The tendency is to avoid open approaches and try to manage a fully endoscopic resection in order to minimize postoperative complications.

We agree that more high level evidence is needed to unify concepts and develop treatment protocols for this rare kind of tumor.

Conflict of interest

The authors declare no conflict of interest.

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