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Case report

Endoscopic management of Ewing's sarcoma of ethmoid sinus within the AMORE framework: A new paradigm

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ABSTRACT

The Ablative MOld and REconstruction (AMORE) protocol developed in the Academic Medical Center of Amsterdam has been used successfully to treat sarcomas. The use of endoscopic surgery fits well within this framework.

A 6-year-old boy presented with Ewing Sarcoma of left ethmoid sinus closest to orbit. The patient underwent neoadjuvant chemotherapy followed by complete endoscopic resection, brachytherapy and reconstruction. Brachytherapy was administered by iridium catheters through limited Lynch–Howarth incision. Skull base defect was reconstructed with a galea flap. The use of endoscopic surgery complemented by neoadjuvant chemotherapy and brachytherapy might maximize tumor control while reducing morbidity.

1. Introduction

Ewing's sarcoma (ES) is part of a class of poorly differentiated malignancies known as peripheral neuroectodermal tumors (pPNETs). First described by Ewing between 1921 and 1939, ES represents the second most common primary malignant bone tumor in children between ages of 10 and 15 years, second only to osteosarcoma. The annual incidence is estimated at 0.6–3-million population, peaks in second decade of life and is slightly common in males (1.5/1) [1]. Most cases affect pelvis and extremities, with only 1–4% of cases involving head and neck region (HN) [1]. The majority of HN-ES occur in the mandible or maxilla, with less than 50 cases of paranasal sinuses and skull base ES described in literature [1,2]. ES is an aggressive disease, presenting with metastases at time of diagnosis in 18–25% of cases [1]. During the past 25 years, 5 year survival of non-metastatic ES has drastically improved, from 10% to 50–65% [1]. This increase in survival is primarily due to a multimodality approach therapy with a combination of surgery, radiotherapy, and chemotherapy. However, External Beam Radiation Therapy (EBRT) can result in marked morbidity with long-term sequelae, which are more prominent in children whose growing tissues and organs in head and neck region are susceptible to radiation damage [3]. In our hospital, a multidisciplinary local treatment protocol consisting of Ablative surgery, MOld technique afterloading brachytherapy and surgical REconstruction termed AMORE protocol [4], has been developed for treatment of pediatric HN malignancies. This protocol has already been applied for managing HN and orbital rhabdomyosarcomas in children with satisfactory outcomes [5–7]. Recently, we have introduced the use of minimally invasive, radical endoscopic skull base surgery for such tumors, with the aim of reducing morbidity while ensuring oncological safety and without compromising outcome. Here, we report a case of an ethmoidal sinus ES treated with endoscopic nasal resection and AMORE protocol at our institution.

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2. Case report

A 6 year-old boy was referred to our institution with recurrent left sided epistaxis and eyelid swelling of one-month duration. He had no other nasal symptoms and no symptoms suggestive of central nervous system involvement. His medical history was significant for adenosine deaminase deficiency (ADA-SCID) syndrome for which he underwent cordblood stemcell transplant, neurosensory deafness, hypothyroidism, epilepsy, recurrent pneumonia and bacterial meningitis. Physical examination demonstrated normal eye movements without proptosis and no evidence of cranial nerve involvement or other neurological impairments. Nasal examination showed a fleshy mass almost completely filling left nasal cavity. Computed tomography with contrast demonstrated a mass completely filling anterior and posterior ethmoids, osteomeatal complex and left nasal cavity with lamina papyracea erosion and orbital extension, as well as thinning of cribriform plate. Magnetic resonance imaging (MRI) with gadolinium contrast showed an expansive lesion, with cystic components, of left ethmoid infiltrating orbital periosteum and of the lamina papyracea (Fig. 1). Biopsy of the mass revealed a cell pattern composed of small cells with heterogenous nuclei, small amount of cytoplasm. Some cells had clear cytoplasm and showed positivity for PAS staining (Glucogen). The cells were concentrated in small areas at multiple sites resulting in an alveolar pattern, suggesting Ewing Sarcoma. Cells were negative for S-100, CD-57. CD-56, desmine, Keratine and were positive for NSE and CD-99. Furthermore, a translocation study was performed confirming ES positive for reciprocal chromosomal translocation between chromosomes 11 and 22; t(11;22)(q24;q12). 99mTc-Bone scintigraphy, Chest-CT and bone marrow punctures did not reveal any evidence of metastases. Therefore, the patient received six courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE), according to EURO-E.W.I.N.G. 99 protocol [8]. After 2 courses of VIDE, a good response was demonstrated by contrast-enhanced MRI (Fig. 2). Following a multidisciplinary meeting, the decision was taken to proceed to wide excision followed by mold brachytherapy, after completion of chemotherapy, according to AMORE protocol [4]. An endoscopic removal was planned, with the proviso that the area resected should target whole mass of original bone tumor together with residual soft tissue mass rather than only residual tumor as evidenced in most recent MRI scan. Surgery took place 5 months after diagnosis and consisted of complete endoscopic resection of crista galli, cribriform plate, lateral lamella and medial orbital wall including periorbita. A Draf 3 was initially performed in order to define anterior limit of skull base resection. The cribriform plate and fovea ethmoidalis, between the orbitae and from the Draf 3 opening to anterior sphenoid wall, was removed. The tumor was left attached on orbit. The dura was widely exposed, but was not removed as not involved by tumor (Fig. 3). A small CSF leak was sealed with a fat plug. The tumor was removed en bloc and intraoperative frozen sections (6 in total) confirmed complete resection with clear margins. A limited Lynch–Howarth incision was performed for placement of brachytherapy catheters, embedded in a thermoplastic synthetic mold (FastForm-percha, Emnovation, B.V., Fig. 4). The brachytherapy was administered reaching an overall dose of 40 Gy in 32 fractions of 1.25 Gy every 2.1 h with pulsed-dose rate afterloading machine to clinical target volume (CTV). The CTV was defined as tissue up to 5 mm from the outer surface of mold, respecting anatomical borders. Surgical reconstruction was performed 10 days after tumor resection, following completion of brachytherapy. At this time, catheters were removed and orbital and skull base defects were reconstructed with a galea flap, inserted through limited Lynch–Howarth incision. The patient was discharged 7 days later and has been disease free until now (12 months). Definitive pathology results showed sound oncological margins and less than 10% vital tumor cells in resected specimen, the latter indicating a good response.

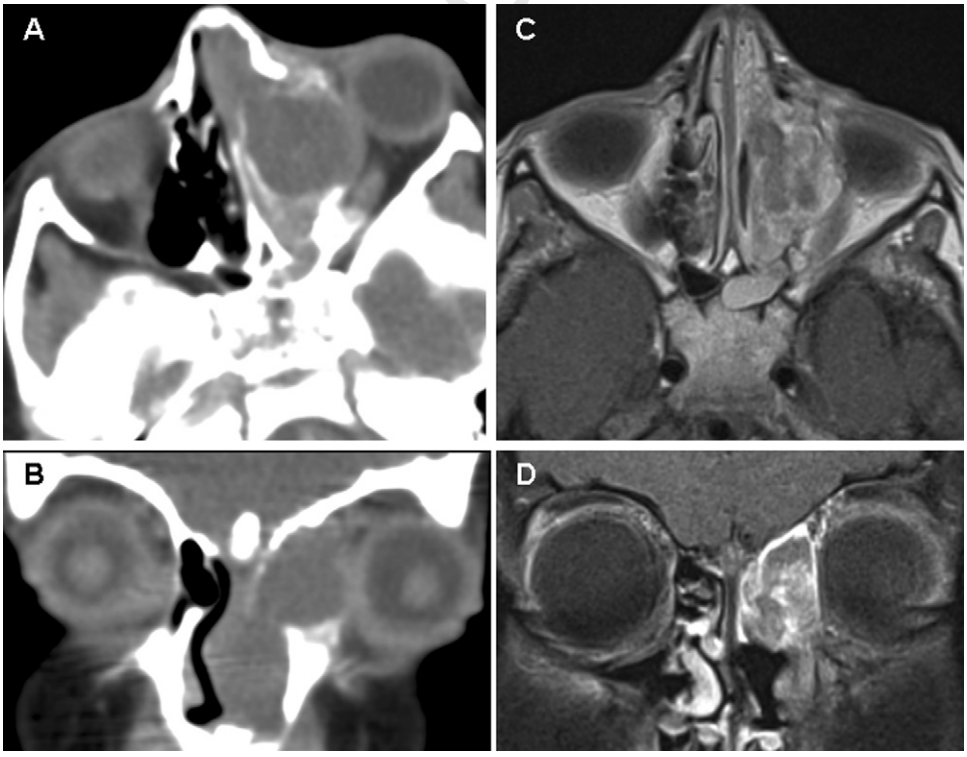

Fig. 1. (A, B) Contrast-enhanced CT scan: an expansile lesion involving ethmoid sinus with displacement of eyeball and edge enhancement was attested. (C, D) Axial and coronal MRI T1 sequence postgadolinium showed the edge enhancement of lesion confined to the sinus ethmoidalis, adjacent to the fovea ethmoidalis. No invasion of orbit, skull base or contralateral side was encountered. Maximum size was 2.6 cm × 1.2 cm × 1.9 cm.

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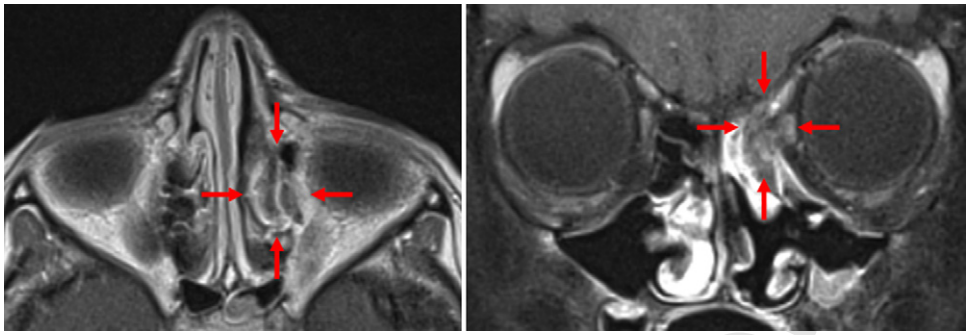

Fig. 2. After 2 cycles of VIDE, MRI T1 sequences postgadolinium demonstrated a reduction of the mass. Maximum size was 2 cm × 0.8 cm × 1.9 cm.

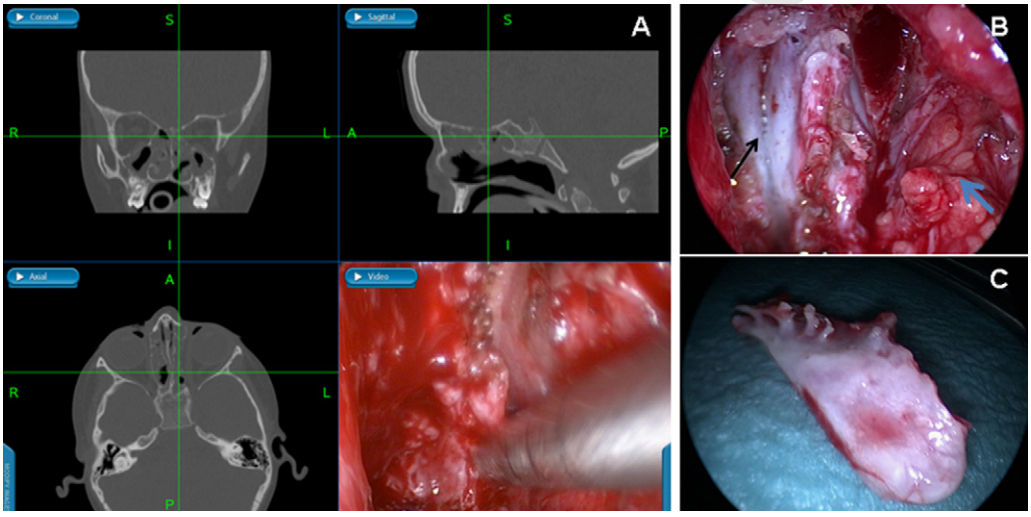

Fig. 3. (A) Navigation system image showed the posterior limit of the resection (sphenoid sinus wall). (B) Endoscopic overview of surgical field after removal of the crista galli, cribriform plate, lateral lamella, medial orbital wall and the periorbita (Black arrow = dura; blue arrow = orbital fat after removal of periorbita). (C) Crista galli, part of surgical specimen.

3. Discussion

ES of bone is a rare entity especially in the HN region. Any surgical approach to HN tumors is challenging. Extensive resections may need to involve important anatomical structures and are often associated with significant functional and cosmetic deformity, especially in children. However, complete excision is vital, if one is to provide the best chances of disease – free survival. A retrospective analysis of 1058 non-metastatic ES patients treated in subsequent European trials showed a better Event Free Survival

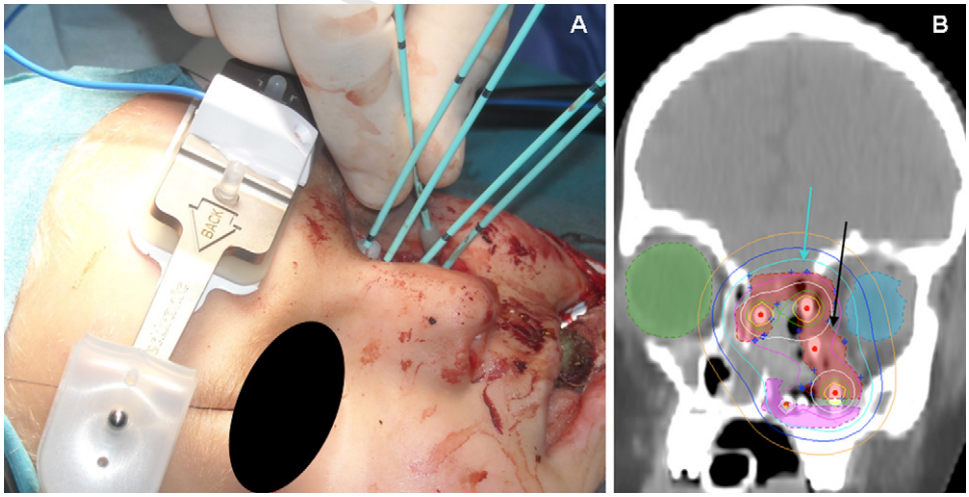

Fig. 4. (A) Brachytherapy catheters, embedded in a thermoplastic synthetic mold, were applied in the surgical field through a limited Lynch–Howarth incision. (B) These catheters were left inside for one week and connected to the after loading machine for dose delivery (the blue arrow indicates the reference isodose 40 Gy: the black arrow indicates the periorbita area).

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(EFS) for patients treated with surgery with or without radiotherapy compared to those who received radiotherapy alone (5 year EFS being 61% and 47% respectively; $p = 0.0001$) [9]. Although such retrospective analyses are open to considerable bias, local treatment guidelines in current ES protocols advocate a non-mutilating wide resection according to Enneking criteria when feasible [10]. In case of a marginal resection postoperative radiotherapy should be added. Debulking or intralesional procedures are discouraged as these have to be followed by additional radiotherapy and do not improve survival compared to definitive radiotherapy alone. A wide oncological resection was regarded unacceptable in our case because of direct mutilating effects. Using modern external beam radiotherapy techniques, target volume uses safety margins of at least 2 cm in all extensions, based on the pre-treatment tumor extent. In our case this would lead to unacceptable local adverse effects concerning the eyes, outgrowth and function of the midface/orbit, and pituitary function. Hence, as is often the case in oncological surgery, one has to balance potentially unacceptable morbidity and a disfiguring procedure against the expected benefits and long term survival. The AMORE protocol has been developed with this in mind, as a way of providing the optimal balance between ablative surgery ("surgery aimed at macroscopical clearance, rather than microscopically clear margins") combined with chemo and brachytherapy followed by reconstruction. Endoscopic techniques that minimise morbidity without sacrificing radicality of removal would in principle lend themselves perfectly to the philosophy of AMORE, as long as adequate access for mold placement with brachytherapy catheters is provided. However, in the past, concerns regarding the suitability of endoscopic techniques, considered as "minimally invasive" have limited their use for malignant tumors. It has been shown however that endoscopic techniques, with clear margins do not necessarily compromise the safety of excision [11]. Indeed, a recent meta-analysis by Devaiah and Andreoli [12] on 361 patients treated for olfactory neuroblastoma showed improved survival for patients treated with endoscopic resection compared with open techniques, although of course, such results must be interpreted with caution. Further, pediatric skull base is incompletely developed and differs anatomically from adult. Nevertheless, most pediatric skull base lesions seem to be suitable for an expanded endoscopic nasal surgery allowing, in oncological terms, satisfactory eradications and good functional and aesthetic results [13]. However, there are few representative studies in literature dealing with pediatric skull base lesions [14,15]. All used a broad spectrum of standardized skull base approaches according to tumor location and type of lesion. What makes ESs more complicated to treat is their wide extension along bone, necessitating often extensive, mutilating procedures. Targeting the original bony mass of the tumor, prior to chemotherapy, is essential, if one is to avoid recurrence. Although comparability of endoscopically and conventionally approached sinonasal and skull base lesions is difficult due to heterogeneity of lesions, complication rate of endoscopic endonasal surgery is very low (around 3%) with few reported permanent deficits. What is part of consensus is that a multidisciplinary team approach is mandatory to obtain good postoperative results.

Even though an expanded endoscopic resection of skull base tumor might allow to remove macroscopical mass, adjuvant radiotherapy will be mandatory in order to eradicate potential microscopic residual of disease, especially closest to vital structures [9]. EBRT is applied routinely in HN malignancies but is known for its long-term sequelae, especially when applied in young children [2]. On the other hand, the advantages of brachytherapy with its focal high dose and rapid dose fall-off beyond the target volume are well established and successfully in the primary treatment of soft-tissue sarcoma, with limited sequelae. Therefore, in our center, AMORE protocol was designed to intensify local treatment and to diminish late radiation sequelae like growth disturbances of craniofacial skeleton, consisting of ablative surgery, intracavitary brachytherapy with a mold technique and surgical reconstruction in two surgical sessions. Total treatment is scheduled in 1 week [4]. This protocol has already been applied for managing HN rhabdomyosarcomas in children with satisfactory outcomes [5–7].

To the best of our knowledge's, this is the first case of skull base/sinonasal ES, treated with endoscopic transnasal surgery and concomitant brachytherapy. Despite the ES involved a portion of left ethmoid sinus, a wide resection of adjacent bone structures was required in order to minimize the rate of local recurrence. At the end of surgery, frozen section from limits of dissection confirmed complete removal. Non-significant complications were noted despite a wide dura exposure and a limited CSF leak that was repaired intraoperatively. Good histological response, radical resection and adequate brachytherapy fields indicate a good prognosis for this patient.

4. Conclusion

Pediatric endoscopic skull base surgery is a proven technique established upon adult skull base experience with low morbidity rates and favorable aesthetic results. Despite certain limitations, current literature would recommend consideration for this approach for many sinonasal and skull base lesions. Moreover, adjuvant brachytherapy may be a reasonable choice in children because of own low rate in long-term sequelae. Nevertheless, further research in a larger cohort is required to determine long-term patient outcomes.

Conflict of interest disclosure

All authors disclose any financial and personal relationships with other people or organizations that could influence the own work.

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