ORIGINAL CONTRIBUTION

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Endoscopy skull-base resection for ethmoid adenocarcinoma and olfactory neuroblastoma*

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SUMMARY

Statement of problem: *Olfactory neuroblastoma (ON) and ethmoid adenocarcinoma (AC) are rare sinonasal malignancies that often involve the skull base. Standard surgical treatment is craniofacial resection (CFR), which allows for efficient removal but entails significant morbidity and mortality. Because expanded endoscopy nasal approaches are newly developed, we aimed to describe the procedure in patients with ON and AC and compare it with CFR in terms of efficiency and morbidity.*

Methods: *This work reports on a retrospective series of 16 patients with AC and ON treated endoscopically with anterior skull-base resection in a single institution over 9 years. Invasion of the frontal sinus, massive extension to the cerebral parenchyma, spread of the tumour above the orbits or lysis of anterior facial skeleton were contraindications for endoscopy resection.*

Results: *Of the 16 patients, 11 had AC and 5 ON. In total, 37.5% (6) exhibited skull-base invasion. All patients had postoperative radiotherapy. In the early postoperative period, one patient experienced delayed seizure due to a minor subdural hematoma. Two delayed complications were observed: one encephalocele related to inappropriate postoperative care, which required revision surgery, and one extended radionecrosis. Five-year disease-free survival was 83% and 5-year recurrence-free survival 58%. Local control rate was 91% for AC and 100% for ON.*

Conclusions: *With low perioperative morbidity and efficient local control, ethmoidectomy combined with anterior skull-base resection is a promising approach for managing selected cases of AC and ON. These findings need further investigation with prolonged follow-up.*

Key words: ethmoid adenocarcinoma, olfactory neuroblastoma, endoscopic resection, anterior skull base

INTRODUCTION

Ethmoid malignancies are rare tumours (1% to 3% of all upper airway tumours) [1,2] with aggressive behaviour (overall 5-year survival 40%-80%) [3]. The treatment of these tumours is difficult and classically requires craniofacial resection (CFR), which combines transcranial and transfacial approaches. CFR has been the gold standard for the removal of these tumours [3], followed by radiotherapy. However, the technique entails significant morbidity, such as pneumatocele, cerebral oedema, cerebral abscess, cerebrospinal fluid leakage, meningitis, stroke and even fatal outcome in up to 4.5% of cases [1].

Ethmoid malignancies comprise a large variety of histological types with heterogeneous prognoses. Of epithelium-derived lesions, the most frequent, at least in Europe, is adenocarcinoma (AC whereas epidermoid carcinoma and sinonasal undifferentiated carcinoma are less frequent. Of neuroectoderm-derived tumours, olfactory neuroblastoma (ON), a malignant neuroectodermal tumour originating from the olfactory membrane of the sinonasal tract, is more frequent and less aggressive than is neuroendocrine carcinoma.

Among these tumours, AC and especially ON are thought to start on the midline of the upper airway. Jankowski et al. found this feature in AC [4], with small lesions mainly observed near the superior turbinate.

Midline tumours are easily accessible by an endoscopy approach, which is why a number of publications have reported on the endoscopy removal of these tumours. However, techniques may vary among centers, and some consider that peeling off the mucosa and periosteum of the sinus and olfactory cleft achieves satisfactory results [4]. However, in 38% of AC and 50% to 75% of ON, the skull base may be involved [5].
This study focused on AC and ON removed endoscopically, with partial or total removal of the anterior skull base and

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postoperative systematic radiotherapy. Three questions were addressed in this work. First, is the resection of the roof of the nasal fossa and cribriform plate warranted for these pathologies? Second, what is the morbidity with endoscopy removal of the anterior skull base? Third, what are the limitations of this endoscopic approach as compared with CFR?

MATERIALS AND METHODS

This was a retrospective study of cases of AC and ON resected by an endoscopy approach with partial or complete removal of the anterior skull base in a single institution, followed by systematic radiotherapy.

Selection Criteria

Cases of AC or ON with invasion of the frontal sinus, massive extension to the cerebral parenchyma, spread of the tumour above the orbits, or lysis of the anterior facial skeleton were considered ineligible for endoscopy resection, as were cases for which endoscopic removal could be achieved with tumour-free margins without skull-base resection. Neck metastasis, if present, was treated simultaneously, but cases of distant metastasis were excluded.

Workup

All patients were clinically investigated for ocular or neurological symptoms, as well as cervical lymph nodes, and risk factors, if any, were reported. Nasal endoscopy was performed in all cases, then biopsy preoperatively on an out-patient basis with the patient under local anesthesia. Computed tomography (CT), magnetic resonance imaging (MRI), body scan or positron emission tomography (PET) were performed to stage the disease and adapt therapy (Figure 1). Tumours were staged according to both the "Union Internationale Contre le Cancer" (International Union Against Cancer [UICC]) (2002) and the Cantù classification [6]. The Kadish classification was not used because it refers to a single type of tumour (ON). ON was staged histologically according to Hyams, which may predict aggressivity and chemosensitivity of the lesion [7]. All patients received treatment according to the cancer committee of our institution and following the recommendations of the French society of OtoRhinoLaryngology. All clinical data were stored in the database of the institution, which is validated by the French council.

Treatment strategy

Neoadjuvant therapy was used for large tumours [8]. Surgery was followed by conformational radiotherapy for all cases.

Follow-up

Follow-up was based on regular endoscopy control of the nasal cavity (every 3 months during the first year and then twice a year), by MRI (Figure 2).

Statistical analysis

Disease- and recurrence-free survival was calculated by the Kaplan-Meier method. Overall survival and disease-free and recurrence time were assessed from the date of surgery to the date of death or first recurrence or of the last control, in the absence of any event. Deaths unrelated to progression of the index tumour were not considered treatment failure, and data for these patients were included in all survival analyses. In disease-free analysis, disease successfully treated for recurrence was not considered treatment failure if patients did not present pathological recurrences at the last control but was considered treatment failure in free-recurrence analysis. Recurrence-rate and symptom prevalence were calculated by simple percent-

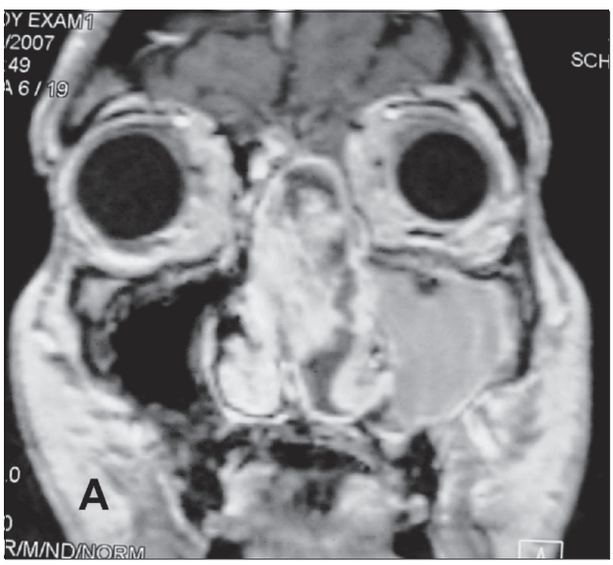

Figure 1. Pre-therapeutic MRI of a case of olfactory neuroblastoma. Gadolinium enhanced T1 weighted coronal view. Notice the bilateral spread of the tumor without obvious intracranial extension.

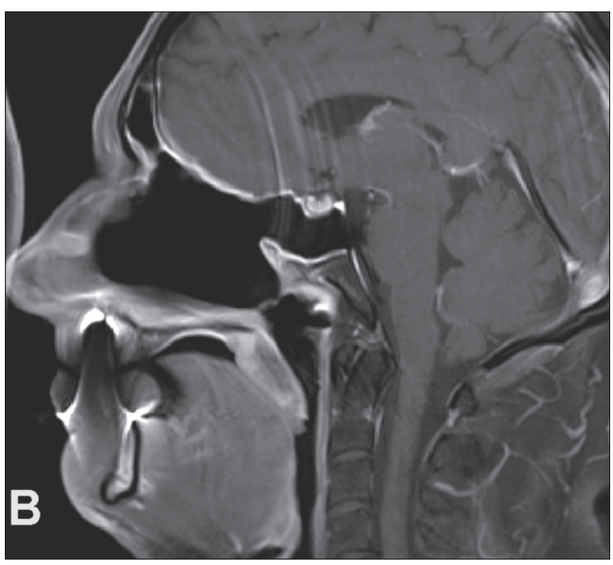

Figure 2 . Post-therapeutic MRI of a case of olfactory neuroblastoma treated through an exclusive endonasal approach with postoperative radiotherapy. T2 weighted sagittal view. The duraplasty can be seen, without herniation. There is no oedema of the frontal lobe.

ages. The follow-up interval was calculated by month, from the date of surgery to the date of the last follow-up.

RESULTS

From 2000 to 2009, 16 patients underwent endoscopy treatment for AC and ON, with partial or complete removal of the anterior skull base (from drilling the cribriform plate to removal of cribriform plates with dura, olfactory bulbs and eventually cerebral parenchyma). In total, 19 patients with tumour extension to the frontal sinus, cerebral parenchyma, above the orbits, or the anterior facial skeleton underwent conventional CFR during the same period. Of the 16 patients operated through the endoscopic approach, 11 had AC and 5 ON (2 grade I, 2 grade II and 1 grade III). All patients with AC were males; 1 with ON was female (sex ratio 2.5). The mean age at the time of diagnosis was 59 years (59.5 years for ON and 58.5 years for AC). In total, 44% of patients used tobacco. By the UICC or Cantù classifications, 7 or 6 tumours were T4, 3 or 1 T3, 5 or 3 T2, and 1 or 6 T1, respectively. Presenting symptoms were nasal obstruction (75%), nasal bleeding (44%), headache (44%), loss of smell (37%), rhinorrhea (6%), self-palpation of a neck mass (6%) or cough (6%) (see Table 1). AC was intestinal in all cases, and all but 1 of the patients were woodworkers. Radiography revealed bony erosion of the anterior skull base in 4 cases of AC and 1 of ON. Four cases showed limited skull base invasion with lysis of the cribriform plate and one case exhibited intradural invasion (AC). Of note, all patients had a single tumour, except for 1 with grade III olfactory neuroblastoma", who presented with 3 distinct tumours (right ethmoid along the orbit, left ethmoid, and floor of the left sphenoid). Neoadjuvant chemotherapy (cisplatin [CDDP] and 5-fluorouracil [5-FU]) was used in 5 cases (3 ON and 2 AC), for medium- or high-grade tumour or when tumour growth was clinically obvious.

Table 1. Presenting symptoms at diagnosis.

Presenting symptoms	
Nasal obstruction	75%
Nasal bleeding	44%
Headache	44%
Loss of smell	37%
Epiphora	18%
Rhinorrhea	6%
Palpation of neck mass	6%
Cough	6%

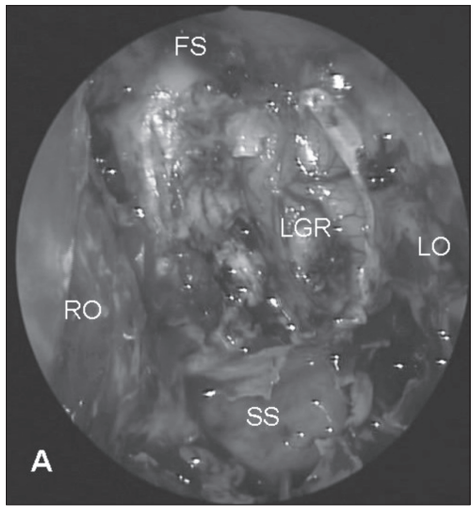

Figure 3. Duraplasty after anterior skull base removal with resection of the right gyrus rectus. The left intact gyrus rectus (LGR) can be seen, as well as the frontal sinus (FS) above and anteriorly, the sphenoid sinus (SS) below and posteriorly, and the left (LO) and right (RO) orbits.

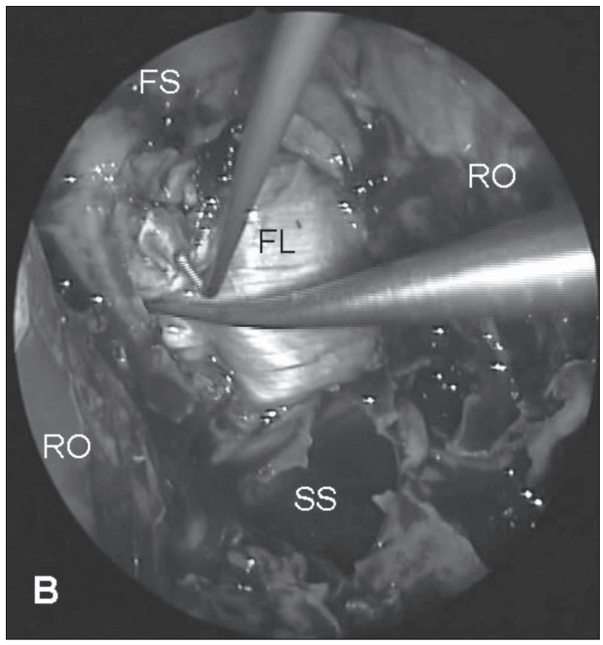

Figure 4. A first layer of fascia lata (FL) is watertight fashioned intracranially and intradurally, while the second layer will be applied extracranially.

Surgical procedure

Surgical strategy was based on centripetal resection and was performed with dedicated instruments (Draf set from Karl Storz GmbH & Co. KG, Tuttlingen, Germany), powered instrumentation and navigation. Surgery started with the definition of the inferior limits of the resection with a laser diode (anterior wall of the sphenoid or rhinopharynx posteriorly, nasal septum medially, lateral wall of the nasal fossa and frontal process of the maxilla anteriorly). Sections were taken and frozen to ensure tumour-free margins. Eventually, debulking of the lesion was performed to obtain a wide field of vision. Dissection was then performed laterally along the orbit in a subperiosteal plane until the ethmoid roof was reached. Small lesions (4 cases) were removed by a unilateral procedure removing one cribriform plate. Most lesions were approached bilaterally: anteriorly by means of a Draf III procedure and posteriorly with removal of the anterior wall of the sphenoid. The dura was then exposed by drilling the roof of the ethmoid. Ethmoidal arteries were coagulated. The crista galli had to be removed before proceeding with the dural resection, which started on the less-affected side. After sectioning the falx cer-

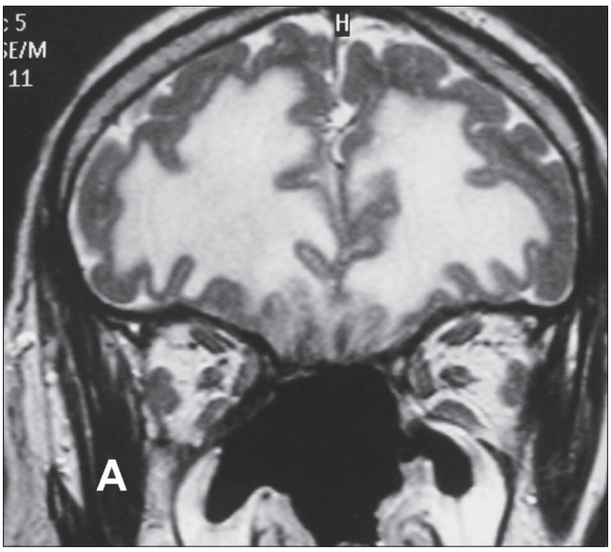

Figure 5. Case of extensive radionecrosis after radiotherapy. This patient was treated two years ago for a triple localization of a high-grade neuroblastoma. On T2-weighted sequences, these coronal slices demonstrate diffuse hypersignal in the frontal lobes which is also present in the basal ganglia.

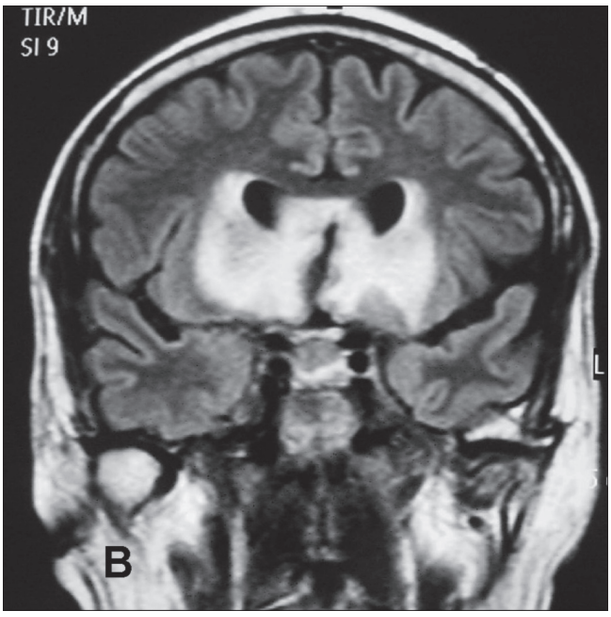

Figure 6. Another feature highly suggestive of radionecrosis.

ebri, the specimen was gently pushed down, which allowed for exposure of the dura from above and resection on the most-affected side. The olfactory bulbs were identified and the olfactory peduncles transected (10 cases). The skull-base specimen was taken out through the nose or through the mouth. If needed, gentle parenchymal resection was achieved on the midline (2 cases). If the tumour adhered to the periorbit, the latter was resected at the end of the procedure, and sections showing limits were frozen. Duraplasty was performed with 2 layers of fascia lata successively fashioned intracranially and intradurally for the first layer and extracranially and extradurally for the second (Figures 3 and 4). Utmost care was given to the positioning of these layers, which had to be watertight. A sheet of Silastic was placed to support the duraplasty for 2 weeks.

Patients underwent CT for visualizing the duraplasty and to eliminate any postoperative bleeding and/or hematoma. One patient with neck metastasis underwent treatment by functional neck dissection before endoscopy and subsequent irradiation. The cancer status of the skull base in cases was as follows: negative (10 cases), involvement of the cribriform plate (4 cases), involvement of the adjacent dura (1 case), and involvement of the cerebral parenchyma (1 case), for 37.5% of cases with skull-base cancer invasion (20% of ON and 45.5% of AC) (see Table 2). Patients received postoperative radiotherapy, with a mean dose of 64 Gy (54 - 72 Gy).

Morbidity

One patient experienced seizures three weeks after being released from hospital. CT revealed a moderate subdural hematoma, which was treated conservatively. Two delayed complications were observed. One patient required duraplasty 3 months after radiotherapy because of previous inadequate endonasal maneuvers performed on the roof of the nasal cavity (removal of adherent crust). Duraplasty then involved an open procedure. The total radiation dose was 54 Gy. The other patient showed extended frontal and pituitary radionecrosis (single case treated with 72 Gy in another institution), with secondary abscess, which required further surgery (Figures 5 and 6).

Tumour control

One patient showed localized recurrence on the inferior turbinate 36 months after surgery, which could be removed by medial maxillectomy. This patient had received the lowest radiation dose. Another patient, who initially presented with cough, showed local tumour progression along the second branch of the trigeminal nerve with rapid invasion of the brainstem within 4 months. This was the single case of AC in a patient not exposed to wood dust.

One case presented skeletal metastasis 1 year after surgery and died due to progression of the lesions despite chemotherapy. Mean follow-up was 21 months. One patient died of an unrelated cause 4 years after surgery. One patient was lost to follow-up.

DISCUSSION

We aimed to investigate endoscopy nasal approaches for ON and AC, rare sinonasal malignancies that often involve the skull base and compare with CFR in terms of efficiency and morbidity. We retrospectively studied 16 cases of AC and ON that were removed endoscopically with partial or total removal of the anterior skull base. The skull base was invaded by disease in 37.5% of cases. Early complications were minimal. Two patients showed delayed local complications: encephalocele after traumatic endoscopic cleaning of the nasal fossa in one and extended radionecrosis in another, which both required revision surgery by a subfrontal approach. We observed 2

local recurrences: one along the second branch of the trigeminal nerve with fatal outcome and one on the inferior turbinate, which could be safely removed endoscopically. One patient died of metastasis despite local control of the disease. The most common lesion was AC of intestinal type (69%), which in 10 of 11 cases, developed in woodworkers. Indeed many authors consider this malignancy an almost exclusively occupational disease.

Limits of the exclusive endonasal approach

Endoscopy resection of sinonasal tumours has obvious limitations that arise from the need for adequate exposure and tumour-free margins. Spread of the tumour inside the frontal sinus or through the dura laterally above the orbits requires a classic subfrontal approach in the case of malignancy. Similarly, significant intradural invasion, even in the midline, might be difficult to safely remove from below. Finally, invasion of the facial skeleton requires a transfacial approach. However, apart from these cases, endoscopy may become the approach of choice for ethmoid lesions, at least for AC and ON. The endoscopy vision allows for defining early and precisely the limits of the mucosal and bony resection, and skull-base resection can be safely performed without craniotomy and subsequent displacement of the frontal lobes. Resection of the periorbit can also be managed this way. Avoidance of craniotomy also prevents osteitis or radionecrosis of the bony flap, which might develop after radiotherapy.

Table 2. Description of the case series.

Histological characteristics	**AC**	**ON**	**All**
n	11	5	16
UICC Classification			
T1	1	0	1
T2	5	0	5
T3	1	2	3
T4	4	3	7
N+	0	1	1
Skull-Base Removal			
CP	2	2	4
CP + DM	2	0	2
CP + DM + OB	5	3	8
CP + DM + OB + CPch	2	0	2
Skull-Base Invasion	5	1	6
Radiological Investigation			
Sensibility	40%	100%	57%
Specificity	67%	100%	80%
Morbidity			
Encephalocoele	1	0	1
Cerebral Radionecrosis	0	1	1
Local recurrence	2	0	2
Distant Metastasis	1	0	1
5 years disease-free survival rate	71%	100%	83%
5-years free-recurrence survival rate	38%	100%	58%
Follow –up	21	21	21

CP: Cribriform Plate; DM: Dura-Mater; OB: Olfactory Bulbs; CPch: Cerebral Parenchyma

Need for skull-base resection

More important than with "en bloc" resection, a technique not feasible for large tumours, the aim of endoscopy should be to ensure that margins are free of tumour. This is an issue difficult to ascertain when the surgical specimen has been fragmented but patients have a better outcome when margins are free of tumour [3,9,10,11]. Thus, biopsies are taken at the limits of resection at the beginning of surgery. Interestingly, the status of the cribriform plate is difficult to evaluate during radiographic workup, as well as during surgery, which warrants systematic resection of the anterior skull base [12], usually selected for only T3 and higher-grade lesions and when the cribriform plate shows tumour [12,13].

To determine the relevance of this option of skull-base resection, we investigated the status of the cribriform plate and dura mater in our patients. Sensitivity of radiographic workup was 57% and seemed to vary by type of tumour. For ON, sensitivity was 100%, which is related to enlargement of the cribriform plate in this pathology. In contrast, for AC, sensitivity was only 40%, probably because of microscopic spread and infiltration of the carcinoma without macroscopic enlargement or lysis of the cribriform plate. Therefore, resection of the skull base seems warranted for tumours that are closely related to the cribriform plate, a conclusion further asserted by no recurrence at the skull base in this series.

Immediate and delayed morbidity

As mentioned earlier, CFR followed by radiotherapy entails significant morbidity [1,3]. The aim of the endoscopy approach is to perform adequate tumour removal and to cause minimal morbidity, which is the goal of minimally invasive surgery.

We observed 1 case of subdural hematoma three weeks after surgery, which may have been caused by excessive traction on the falx cerebri in initiating the upper resection. Luckily, this complication could be managed conservatively. The surgical technique was later modified to prevent this traction, and the crista galli was removed separately before proceeding with dissection or resecting the dura.

With duraplasty, we found no cases of immediate cerebrospinal fluid leakage following skull-base resection. However, one patient showed encephalocele and cerebrospinal fluid leakage because of inadequate intranasal cleaning in another institution weeks after radiotherapy. Insertion of a vascularized flap, such as a pericranial flap by minimally invasive endoscopy [14], may have prevented this complication, because crusting is common during the healing process in nasal cavities. A nasoseptal flap [15] could not have been considered in this case because of septal invasion by the tumour.

A delay between surgery and radiotherapy should be emphasized because radiotherapy in this series was regularly initiated early after surgery, 6 weeks, on average, while the nasal cavity and skull base reconstruction was not fully covered by mucosa. Finally, the radiation dose delivered after surgery should be < 65 - 68 Gy so as to avoid extensive radionecrosis, as occurred in 1 of our cases. This patient had received 72 Gy because of triple localization of ON, with a wide field of irradiation,

because 1 tumour was on the floor of the sphenoid sinus.

Follow-up (survival and local control)

Kaplan-Meyer analysis revealed the survival rate with endoscopy for AC and ON without disease to be 83% at 5 years and recurrence-free survival 58% at 5 years. With the standard, CFR [3], a collaborative study reported a 53.1% recurrence-free survival rate for AC and 64.3% for ON. To support the relevance of the endoscopy approach, further studies should involve more patients and a longer follow-up, although in our series, 69% of cases were T3-T4 according to the UICC classification. Of note, several works have recently supported this approach [4,16,17,18], even without skull-base resection [19].

Two cases showed local recurrence: one was on the nasosinusal wall and could be easily managed endoscopically 3 years after initial treatment. Medial maxillectomy performed at the time of initial treatment might have prevented recurrence. The second recurrence was related to the spread of the tumour to the middle fossa along the second branch of the trigeminal nerve. Indeed, the large study of the collaborative group [3] revealed that combined anterior and middle cranial-fossa involvement is an independent predictor of recurrence, as is brain or intraorbital invasion.

Obviously, longer follow-up is needed to further ascertain the relevance of endoscopy for AC and ON, with 5-year survival rates examined by Kaplan-Meier analysis. Long-term results will be reported.

CONCLUSIONS

With a low rate of perioperative morbidity and efficient local control of the disease, ethmoidectomy combined with anterior skull-base resection is a promising approach for managing selected cases of AC and ON. This conclusion needs to be confirmed by prolonged follow-up.

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