Intestinal type adenocarcinoma of the ethmoid: Outcomes of a treatment regimen based on endoscopic surgery with or without radiotherapy

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ABSTRACT: *Background.* The purpose of this study was to assess survival, prognostic factors, and complications in a cohort of patients with intestinal-type adenocarcinoma (ITAC) treated with transnasal endoscopic surgery ± radiotherapy (RT).

Methods. Patients with ITAC who underwent endoscopic surgery ± RT at 2 tertiary centers were retrospectively reviewed. Overall survival (OS) and event-free survival were calculated, and statistically significant variables were entered in a multivariate Cox regression model. Complications were also analyzed.

Results. One hundred-sixty-nine patients were included. Major complications occurred in 9.5% of patients. Adjuvant RT was delivered in 58.6% of patients. Five-year OS and event-free survival were 68.9% and 63.6%, respectively. Advanced pT classification, high-grade, and positive surgical margins were independently predictive of poor survival.

Conclusion. Endoscopic surgery ± RT is a valid treatment option in most cases of ITAC. When compared with series based on external surgery, our results support a definitive paradigm shift in the management of ITAC. © 2015 Wiley Periodicals, Inc. *Head Neck* **38**: E996–E1003, 2016

KEY WORDS: intestinal-type adenocarcinoma, endoscopic surgery, ethmoid, sinonasal tumors, endoscopy

INTRODUCTION

According to the World Health Organization,[1] adenocarcinomas of the sinonasal tract are classified in 2 main groups: intestinal type and non-intestinal type. Intestinal-type adenocarcinoma (ITAC) presents some characteristic features as follows: (1) it arises from the olfactory niche[2]; (2) it is found in the overwhelming majority in patients with exposure to hardwood dust or leather tannins[3]; and (3) has a limited tendency to be associated with regional and distant metastases at presentation. The unique epidemiologic and histologic features of ITAC, compared to non-ITAC, require that data on the 2 groups of tumors be analyzed separately. However, this conflicts with the rarity of the disease, and that only very few reports specifically focus on the management of ITAC.[4–6]

Although a chemotherapy regimen based on cisplatin, fluorouracil, and leucovorin has been shown to be highly effective in ITAC with wild-type or functional p53 protein,[7] surgery followed by radiotherapy (RT) is considered the standard of care. A major step forward in the refinement of surgical strategy was the introduction of anterior craniofacial resection in the 1960s,[8] which is a combined transfacial-transcranial technique that enables obtaining clear margins at the intracranial level in tumors involving the anterior skull base. Anterior craniofacial resection, together with other external techniques suitable for early lesions, has remained the gold standard for the resection of nasoethmoidal malignancies for some decades and, specifically, of ITAC.[4] This principle began to be challenged in the late 2000s when the first large experiences[9–11] in the management of malignant tumors of the nasoethmoid with endoscopic surgery were reported. However, because ITAC was grouped together with other histologies, no data concerning specific survival and prognostic factors were provided. Very recent observational studies[5,12,13] seem to suggest that a treatment schedule for ITAC, including endoscopic surgery ± RT, offers survival outcomes similar to those reported in historical series of patients treated with external surgery ± RT.

The present retrospective study was designed to study the overall survival (OS) and event-free survival together with the complications in a series of 169 patients with ITAC of the ethmoid treated with different forms of endoscopic resection ± RT at 2 tertiary referral centers. Factors affecting OS, event-free survival, and complications were also investigated.

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PATIENTS AND METHODS

Patient selection and workup

After approval by the respective ethics committees, clinical data (age at diagnosis, sex, occupational history,

previous treatment, preoperative workup, type of surgery, complications, histologic findings, adjuvant treatment, postoperative staging, relapse of the disease, re-treatment, and follow-up) on patients with ITAC of the ethmoid undergoing curative treatment with endoscopic resection ± RT at the Departments of Otorhinolaryngology of the Universities of Brescia and Varese from October 1997 to September 2013 were retrieved from a dedicated database.

All patients had undergone complete clinical examination, routine blood counts, liver function tests, and were staged by multiplanar CT and contrast enhanced MRI (or contrast-enhanced CT whenever an MRI could not be obtained), chest X-ray, and, since 2008, positron emission tomography/CT in advanced-stage lesions. After imaging evaluation, a biopsy with the patient under local anesthesia was obtained. Treatment planning was discussed by the local multidisciplinary team at the 2 centers, based on a common management strategy.

Surgery

Patients were treated by 3 different surgical approaches (endoscopic resection without or with transnasal craniectomy [ERTC], or cranioendoscopic resection) based on the local extent of disease. Surgical techniques are described in detail elsewhere.[9,14,15] Lesions without any critical relationship with the orbit and anterior skull base were considered amenable to endoscopic resection. Contact with or limited infiltration of the anterior skull base, focal infiltration of the dura, with or without limited intradural extension, were considered indications for ERTC, which included the resection of the anterior skull base between the 2 laminae papyracea and from the posterior wall of the frontal sinus back to the planum sphenoidale, the overlying dura, and olfactory bulbs and tracts. Tumors with minimal extension to the brain, without surrounding edema on MRI or critical relationship with major cerebral vessels, were also managed endoscopically. Only in selected cases of strictly lateralized lesions in focal contact with the anterior skull base was the procedure limited to the affected side to preserve contralateral olfactory structures. Lesions with anterior or lateral involvement of the frontal sinus, infiltration of the dura far over the orbital roof, or extensive infiltration of the brain were managed by combining the endoscopic approach with subfrontal craniotomy (cranioendoscopic resection).

Erosion of nasal bones or floor of the nasal cavity, extensive involvement of the lacrimal pathway (except the nasolacrimal duct), infiltration of the walls of the maxillary sinus (except the medial one), and invasion of the orbital content, were considered absolute contraindications for an endoscopic approach.

Treatment of the neck was performed only in patients who presented clinical and radiological positive nodes at diagnosis.

Histologic findings and postoperative staging

Tissue blocks were retrieved, and histologic slides were examined by a senior pathologist (L.M.) to confirm the diagnosis of ITAC, and assess grade (1 = well-differentiated; 2 = moderately differentiated; and 3 = poorly differentiated).

Surgical and histologic reports were analyzed, and all lesions were retrospectively staged according to the TNM classification.[16]

Adjuvant therapy

Although advanced stage, poor differentiation, and presence of positive surgical margins were the main factors considered, the indication for adjuvant RT was discussed for each patient by the multidisciplinary team, also taking into account age, comorbidities, previous treatments, and, especially for low-stage ITAC, the availability of the patient for adequate follow-up.

Follow-up

All patients were followed according to our institutional protocols, which included endoscopic evaluation and MRI every 2 and 4 months, respectively, during the first year, both endoscopic evaluation and MRI every 6 months until the fifth year, and clinical evaluation and MRI yearly thereafter. In recent years, yearly positron emission tomography/CT was introduced in the follow-up of advanced-stage lesions.

Statistical analysis

OS was defined as the time from surgery to death for all causes, whereas event-free survival was defined as the time from surgical treatment until relapse (any site) or death of all causes. Both OS and event-free survival were determined from the date of diagnosis of ITAC to the end of follow-up, which was November 30, 2013. Vital status at the end of the follow-up and causes of death were ascertained for all subjects.

Cumulative survival curves were modeled using the Kaplan–Meier method with Greenwood SE. The association of 8 variables (sex, age, pT classification, grade, dural involvement, brain involvement, surgical approach, and adjuvant RT) with patient survival was tested by univariate analysis using the log-rank test. In addition, the same variables were tested by multivariate analysis using Cox proportional hazard models, which provided estimates of hazard ratios (HRs), 95% confidence intervals (CIs), and p values using the Wald test. We also conducted a competing risk analysis using non-ITAC related deaths as a competing event. The results were summarized with subdistribution HRs, 95% CIs, and p values.

Graphical control on each regressor did not detect major departures from the proportional hazard assumption of the models. For statistical tests, p values $< .05$ were considered significant in 2-tailed tests. All statistical analyses were carried out using STATA software, version 12.0 (STATA Statistics/Data Analysis 12.0; STATA Corporation, College Station, TX).

The associations of postsurgical complications with clinical and demographic features were also analyzed using a multivariate logistic regression model. The results are reported as odds ratios and 95% CIs.

TABLE 1. Demographic and clinicopathological characteristics, type of surgery and adjuvant therapy, recurrence, and patients status at the end of the follow-up in 169 patients with intestinal-type adenocarcinoma.

Characteristic	No. of patients	%
Total	169	
Sex		
Male	151	89.3
Female	18	10.7
Exposure type ($n = 156$)		
None	28	17.9
Wood dust	82	52.6
Leather dust	46	29.5
Previous treatment		
None	127	75.1
Surgery	17	10
Surgery, RT	12	7.1
Surgery, RT, chemotherapy	4	2.4
RT	4	2.4
RT, chemotherapy	3	1.8
Chemotherapy	2	1.2
Surgical approach		
Endonasal endoscopic resection	38	22.5
ERTC	103	60.9
Cranioendoscopic resection	28	16.6
pT classification		
T0	1	0.6
T1	34	20.1
T2	48	28.4
T3	32	18.9
T4a	11	6.6
T4b	43	25.4
pN classification		
N0	166	97.6
N1	1	0.6
N2a	0	0
N2b	2	1.2
N2c	0	0
N3	1	0.6
Surgical margins		
Negative	151	89.4
Positive	18	10.6
Grade		
1	24	14.2
2	109	64.5
3	36	21.3
Dural involvement		
None	137	81.7
Present	31	18.3
Brain involvement		
None	159	94.1
Present	10	5.9
Adjuvant therapy		
None	69	40.8
RT	99	58.6
Recurrence		
None	133	78.6
Local	16	9.5
Leptomeningeal	3	1.8
Distant	2	1.2
Local, distant	6	3.5
Distant, leptomeningeal	4	2.4
Local, regional	3	1.8
Local, leptomeningeal	2	1.2
Status		
NED	114	67.4
AWD	4	2.4
DOC	21	12.4
DOD	30	17.8

Abbreviations: RT, radiotherapy; ERTC, endoscopic resection with transnasal craniectomy; NED, no evidence of disease; AWD, alive with disease; DOC, dead of other causes; DOD, died of disease.

RESULTS

Patient data

A total of 169 patients (89.3% men) with a mean age of 66 years (SD = 10.3) were identified (Table 1). Some of these patients had already been included in previous studies.[9,13,14] Although professional employment data were missing in 13 patients (7.7%), the majority of patients (82.1%) had a history of professional exposure to wood or leather (28.5 mean years of exposure; range, 2–66 years) and 46.5 mean years of latency (range, 11–72 years). A total of 127 patients (75.1%) had not received any previous treatment, whereas 42 (24.9%) were referred for recurrent ($n = 31$; 8.3%) or persistent ($n = 11$; 6.5%) disease.

Surgery

ERTC, performed in 103 patients (60.9%), was the most commonly adopted procedure for treatment of the primary lesion (Table 1). Unilateral resection of the anterior skull base was performed in only 14 cases (8.3%), whereas the overwhelming majority ($n = 89$; 91.7%) underwent bilateral resection. In 2 cases (1.2%), the resection was extended to the brain.

Unilateral selective neck dissection (levels II–V) was performed in 4 patients with ipsilateral lymph node metastasis.

Pathologic findings and postoperative staging

Pathologic T classification was distributed as follows: 1 (0.6%) pT0; 34 (20.1%) pT1; 48 (28.4%) pT2; 32 (18.9%) pT3; 11 (6.6%) pT4a; and 43 (25.4%) pT4b (Table 1). The patient with a pT0 tumor had been previously treated at another hospital for a pT3N0M0 tumor with positive surgical margins. In 4 patients with a clinically positive neck, pathologic staging was pT4bN1M0G2, rpT4bN1M0G2 (recurrence after previous surgery), rpT4bN2bM0G2 (persistence after previous surgery), and rpT2N3M0G3 (recurrence after previous surgery and RT). No concomitant distant metastases were detected.

Positive surgical margins were identified in 18 patients (10.6%; 14 pT4b [8 dura, 5 orbital apex, 1 nasopharynx]; 3 pT3 [nasal cavity]; and 1 pT4a [sphenoid]).

Distribution by histologic grade was as follows: 24 patients (14.2%) had a well-differentiated lesion, 109 patients (64.5%) had a moderately differentiated lesion, and 36 patients (21.3%) had a poorly differentiated lesion.

Adjuvant therapy

Adjuvant RT on the primary site with different techniques was delivered in 99 of 169 patients (58.6%; 99 of

TABLE 2. Complications and their management.

Complications	No. of patients	%	Treatment
Early	22	13	
Major	15	8.9	
CSF leak	8	4.7	2 revision surgeries 2 revision surgeries and lumbar drainage 3 lumbar drainage 1 spontaneous resolution
Brain abscess	3	1.8	Surgical drainage
Ictus cerebri	1	0.6	Medical therapy
Unilateral loss of vision	1	0.6	None
Pneumocephalus	1	0.6	Revision surgery
Pulmonary embolism	1	0.6	Medical therapy
Minor	7	4.1	
Transient diplopia	3	1.8	None
Seroma	1	0.6	None
Local infection	2	1.2	Medical therapy
Transient disorientation	1	0.6	None
Late	7	4.1	
Major	1	0.6	
Frontal osteomyelitis	1	0.6	Medical therapy
Minor			
Epiphora	3	1.8	3 dacryocystorhinostomy
Mucocele	3	1.8	3 surgical drainage
Total	29	17.1	

Abbreviation: CSF, cerebrospinal fluid.

147 patients [67.3%] excluding those previously treated with RT): conformal 3D in 60 (60.6%), intensity-modulated RT in 36 (36.4%), and external beam in 3 (3%). If patients previously treated with RT are excluded, 61 of 70 (87.1%) of pT3 to pT4 and 38 of 77 (49.8%) of pT1 to pT2 underwent adjuvant RT. The dose ranged from 50 to 66 Gy. In 13 patients (10 pT4b, 3 pT4a), elective RT on the neck (50 Gy) was added.

Complications and hospitalization

Early and late complications (grouped as major and minor) and their management are summarized in Table 2. Twenty-two patients (13%) and 7 patients (4.1%) experienced early and late complications, respectively. Overall, cerebrospinal fluid (CSF) leak, with 8 cases (4.7%), was the most commonly observed complication (5 of 103 [0.5%] ERTCs, and 3 of 28 [10.7%] cranioendoscopic resections). Among late complications, epiphora because of lacrimal pathway obstruction and mucocele, occurring in 3 patients (1.8%) each, were the most frequently encountered. No perioperative death was observed. The mean hospitalization time was 14.2 days (range, 2–125 days).

Follow-up

No patient was lost to follow-up. The median follow-up was 42.8 months (range, 1–170 months).

After a median of 13 months, 36 patients (21.3%) developed relapse (9.5% local, 1.8% leptomeningeal, 1.2% distant, 3.5% local and distant, 2.4% distant and leptomeningeal, 1.8% local and regional, and 1.2% local and leptomeningeal). Distant metastases were distributed as follows: brain 3.6%, bone 2.4%, lung 2.4%, and liver 1.2%. Six patients showed distant recurrences at multiple sites. Twenty-one patients (58.3%) with local or locoregional recurrence were treated with curative intent (8 [38%] endoscopic approach, 4 [19%] endoscopic approach + RT, 4 [19%] external approach, 4 [19%] external approach + RT, and 1 (5%) endoscopic approach + neck dissection + RT). Seven of these patients (33%) had a second relapse (4 local, 1 regional, 1 distant, and 1 distant and leptomeningeal) after a median of 24 months. Only 4 patients (57.1%) with a second relapse were treated (2 external approach + chemotherapy, 1 external approach, and 1 external approach + RT).

Statistical analysis

The curves of OS and event-free survival are shown in Figure 1. At 1, 3, and 5 years, OS was 93.0%, 80.5%, and 68.8%, respectively, whereas event-free survival was 85.2%, 73.3%, and 71.7%, respectively. The results of univariate analysis are summarized in Table 3. Grade, pT classification, dural and brain involvement, surgical approach, and positive surgical margins significantly impacted both OS and event-free survival. The statistically significant prognostic factors for OS and event-free survival using Cox regression models, and those associated with a risk of death from ITAC-related causes, using a competing risk model, are shown in Table 4. The pT4b versus pT1 to pT2 classification, G3 versus G1, and positive versus negative surgical margins were independently associated with a higher risk of death in all models. The risk of death was roughly twice that for pT3 to pT4a than for pT1 to pT2 tumors, which was statistically significant only when considering the event-free survival model. Dural involvement was excluded from the final model

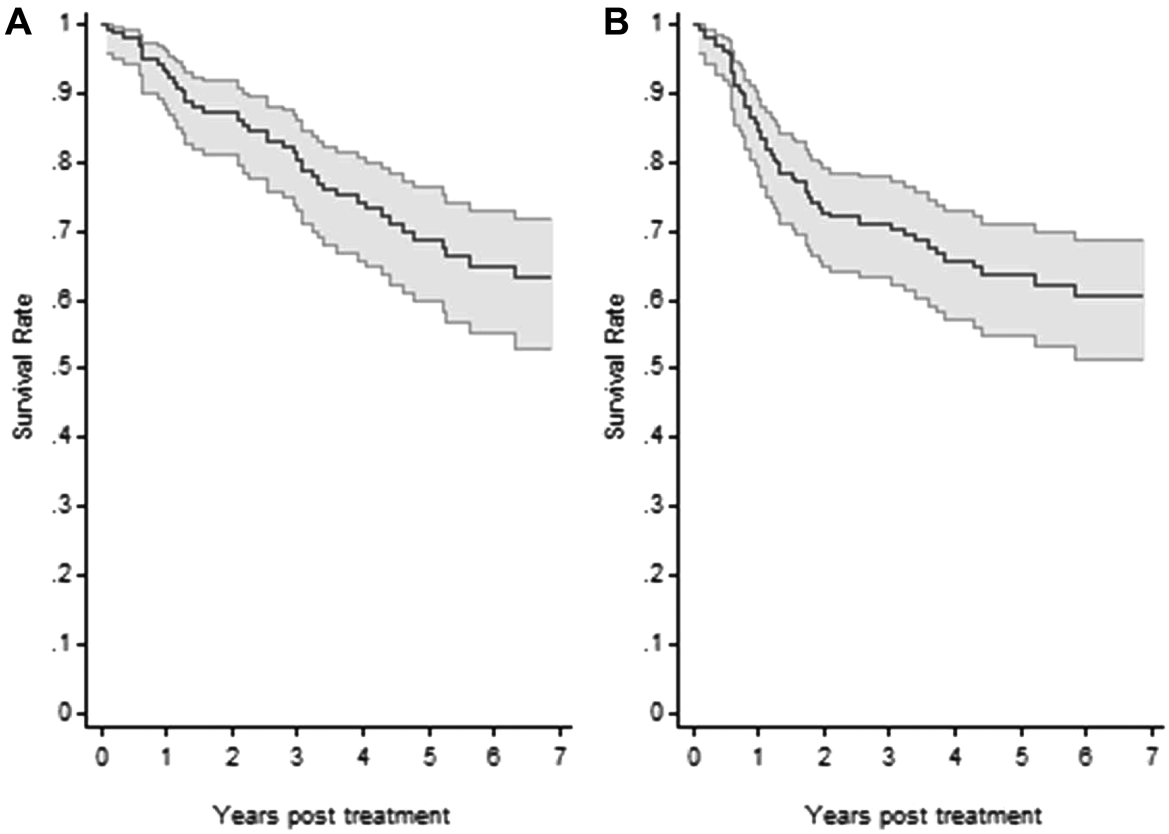

FIGURE 1. Overall (A) and event-free (B) survival.

because of collinearity with pT classification; however, when excluding pT classification from the model, dural involvement was not associated with the risk of death in all models (data not shown).

The occurrence of complications was significantly associated with pT4b classification, dural involvement, and surgical approach, but not with sex, age, or other variables (Table 5). In multivariate logistic regression analysis, only cranioendoscopic resection compared to endonasal endoscopic resection was associated with a higher risk of complications, when also adjusting for pT classification (odds ratio = 15.4; 95% CI = 2.81–84.7; $p = .002$; data not shown).

Mean hospitalization time was significantly associated with the surgical approach (endonasal endoscopic resection 7.4 days, ERTC 14.1 days, and cranioendoscopic resection 26.3 days; $p < .001$).

DISCUSSION

This retrospective study reports the results of a treatment regimen based on endoscopic surgery ± RT on 169 consecutive patients affected by ITAC, which is the largest cohort of this rare disease reported to date. The major strength of our study was that patients were treated at 2 university hospitals according to the same strategy in terms of workup, treatment philosophy, surgical technique, and posttreatment surveillance in a relatively short time span. In the absence of any possibility to plan a prospective study comparing external and endoscopic surgery, which would be considered unethical, our results, together with those of 3 recent studies,[5,6,12] provide evidence-based support for the use of endoscopic surgery, planned according to precise indications and contraindications, as the surgical treatment of choice for ITAC.

The distribution of patients in our study and those from Vergez et al[12] and Camp et al[5] in relation to T and N classification was quite similar, with only a slightly lower proportion of locally advanced lesions in the Belgian study.[5] The major difference between the previous and present study lies in the fact that we also included patients with residual/recurrent lesions; this was deliberately done to see if this factor had an impact on prognosis. The comparative analysis of survival data show remarkable similarities. Five-year OS was 68.8% in our series and 62% and 68% in the studies of Vergez et al[12] (2013) and Camp et al[5] (2014), respectively. Comparable rates of 5-year event-free survival were observed herein (71.7%) and in the French study (74%).[12] The less favorable proportion of 62% reported by Camp et al[5] correlates well with a higher prevalence (38%) of recurrence and possibly reflects a more conservative surgical attitude in tumors involving the anterior skull base.

The comparison of series based on endoscopic surgery with historical studies, including external approaches, is hampered by the absence of stratification between ITAC and non-ITAC.[17–19] Only Cantu et al[4] specifically addressed the outcome of a treatment schedule based on external surgery in patients with ITAC and reported a

TABLE 3. Overall and event-free survival (percentage ± SE) at 1, 3, and 5 years after diagnosis of intestinal-type adenocarcinoma according to various prognostic factors and univariate analysis using the log-rank test.

	% OS				% Event-free survival			
Variables	1 y	3 y	5 y	*p* value	1 y	3 y	5 y	*p* value
Total	93.0 ± 2.0	80.5 ± 3.3	68.8 ± 4.2		85.2 ± 2.9	71.7 ± 3.7	64.0 ± 4.2	
Sex								
Male	92.1 ± 2.3	78.6 ± 3.7	66.3 ± 4.7	NS	82.6 ± 3.2	68.2 ± 4.1	60.4 ± 4.6	**.039**
Female	100	94.4 ± 5.4	86.6 ± 9.0		100	94.4 ± 5.4	86.6 ± 9.0	
Age, y								
<60	91.6 ± 4.6	84.3 ± 6.6	79.8 ± 7.6	NS	85.7 ± 5.9	82.4 ± 6.5	82.4 ± 6.5	
60–69	97.7 ± 2.3	78.8 ± 6.7	61.1 ± 8.8		85.7 ± 5.4	65.0 ± 7.6	49.5 ± 9.0	NS
≥70	90.0 ± 3.6	79.0 ± 5.0	68.9 ± 6.1		82.9 ± 4.5	70.8 ± 5.5	65.2 ± 5.9	
Professional exposure								
No	100	90.8 ± 6.2	84.7 ± 8.3	NS	95.8 ± 4.1	86.5 ± 7.3	80.3 ± 9.0	**< .043**
Yes	92.5 ± 2.4	80.7 ± 3.8	68.2 ± 5.1		83.2 ± 3.4	69.1 ± 4.4	62.1 ± 4.9	
Previous treatments								
No	93.9 ± 2.2	80.9 ± 3.9	70.2 ± 4.9	NS	89.7 ± 2.8	73.6 ± 4.2	65.7 ± 4.9	NS
Yes	89.9 ± 4.8	78.9 ± 6.7	64.8 ± 8.5		69.8 ± 7.3	64.2 ± 7.7	57.2 ± 8.3	
Grade								
1	100	89.3 ± 7.2	89.3 ± 7.2		100	90.5 ± 6.4	90.5 ± 6.4	
2	96.1 ± 1.9	87.1 ± 3.5	73.5 ± 5.1	**< .001***	89.2 ± 3.1	77.3 ± 4.3	66.7 ± 5.3	**< .001***
3	80.5 ± 7.2	51.7 ± 10.1	33.5 ± 10.8		60.7 ± 8.9	37.0 ± 9.3	30.8 ± 9.6	
pT classification								
T1–T2	98.7 ± 1.3	92.8 ± 3.1	86.5 ± 4.6	**< .001***	94.8 ± 2.6	87.7 ± 3.8	81.5 ± 5.0	**< .001***
T3–T4a	95.2 ± 3.3	89.5 ± 5.0	66.6 ± 9.0		83.2 ± 5.8	71.9 ± 7.3	56.5 ± 8.9	
T4b	78.7 ± 6.7	46.5 ± 8.5	36.0 ± 8.5		65.2 ± 7.8	36.6 ± 8.1	33.6 ± 8.0	
Dura involvement								
No	96.8 ± 1.6	88.5 ± 3.0	75.3 ± 4.5	**< .001**	88.8 ± 2.8	79.2 ± 3.7	69.5 ± 4.6	**< .001**
Yes	75.7 ± 8.0	49.2 ± 9.7	43.8 ± 10.0		65.3 ± 8.9	39.9 ± 9.3	39.9 ± 9.3	
Brain involvement								
No	95.9 ± 1.6	84.2 ± 3.2	72.7 ± 4.3	**< .001**	87.6 ± 2.7	75.6 ± 3.7	67.4 ± 4.3	**< .001**
Yes	50.0 ± 15.8	25.0 ± 14.8	12.5 ± 11.5		40.0 ± 15.5	–	–	
Surgical approach								
Endoscopic resection	100	90.9 ± 5.0	77.9 ± 7.4	**< .001***	94.6 ± 3.7	88.9 ± 5.3	75.7 ± 7.5	
ERTC	95.7 ± 2.1	83.1 ± 4.2	75.1 ± 5.4		87.0 ± 3.5	73.8 ± 4.7	68.2 ± 5.3	**< .001***
Cranioendoscopic resection	73.1 ± 8.7	57.7 ± 9.7	42.3 ± 9.7		61.5 ± 9.5	38.5 ± 9.5	34.6 ± 9.3	
Surgical margins								
Negative	96.3 ± 1.6	87.0 ± 3.1	77.1 ± 4.1	**< .001**	90.5 ± 2.5	78.6 ± 3.6	70.9 ± 4.3	**< .001**
Positive	66.7 ± 11.1	32.4 ± 11.3	13.0 ± 8.4		38.9 ± 11.5	16.7 ± 8.8	8.3 ± 7.3	
Adjuvant radiotherapy								
No	94.2 ± 2.8	85.3 ± 4.6	71.2 ± 6.5	NS	82.6 ± 4.6	73.1 ± 5.5	63.2 ± 6.6	NS
Yes	92.0 ± 2.9	76.4 ± 4.8	66.4 ± 5.7		86.2 ± 3.7	69.7 ± 5.1	63.4 ± 5.5	

Abbreviations: OS, overall survival; NS, not significant; ERTC, endoscopic resection with transnasal craniectomy.
* Log-rank test for trend.
The sample size was too small for Kaplan–Meier analysis.
The figures in bold indicate statistical significance.

5-year crude cumulative incidence of disease relapse of 51%. This cohort of 153 patients included a high proportion of T3 to T4 lesions (76.5%) and 66.7% of patients had residual/recurrent tumor, which could explain the high rate of treatment failures.

The missing link in the comparison between the efficacy of external and endoscopic approaches has been provided by a recent single institution, retrospective, comparative study.[6] By analyzing 2 groups of patients with ITAC that were homogeneous in terms of stage, histologic findings, and adjuvant therapy, treated with an external ($n = 31$) or endoscopic ($n = 43$) approach, Grosjean et al[6] observed a 3-year OS of 61.3% and 76.7%, respectively. Although these data need to be cautiously interpreted in view of the limited sample size, they seem to suggest that endoscopic surgery provides oncologic results that are at least as good as those of external surgery.

Multivariate analysis of factors affecting prognosis of ITAC has not been performed to date. In our series, we identified pT category, status of surgical margins, and tumor grade as significant prognostic factors for both OS and event-free survival. Our decision to classify tumors according to the histologic grade instead of using Barnes subtype classification[20] was based on the results of a study conducted on a selected group of patients[13] from our series, which found that Barnes classification,[20] in contrast to tumor grade, was not predictive of prognosis. However, we believe that there is an absolute need to prospectively assess the prognostic value of different histological parameters (ie, grade, subtype), based on a

TABLE 4. Multivariate Cox regression and competing risks models with intestinal-type adenocarcinoma-related causes of death as outcome.

	Cox regression model OS		Cox regression model Event-free survival		Competing risk model	
Category	HR (95% CI)*	*p* value	HR (95% CI)*	*p* value	Sub-HR (95% CI)*	*p* value
pT classification						
T1–T2	Ref.		Ref.		Ref.	
T3–T4a	1.92 (0.85–4.34)	NS	2.10 (1.03–4.25)	**.040**	2.57 (0.64–10.30)	NS
T4b	3.15 (1.39–7.14)	**.006**	2.35 (1.10–5.02)	**.027**	6.24 (1.64–23.80)	**.007**
Grade						
1	Ref.		Ref.		Ref.	
2	1.70 (0.59–4.9)	NS	2.35 (0.82–6.71)	NS	2.57 (0.60–11.02)	NS
3	3.31 (1.06–10.35)	**.040**	4.52 (1.44–14.19)	**.010**	5.69 (1.08–29.88)	**.040**
Surgical margins						
Positive vs negative	3.50 (1.71–7.18)	**.001**	3.29 (1.63–6.64)	**.001**	5.33 (2.15–13.22)	**< .001**

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; Ref., reference; NS not statistically significant $p > .5$.
* Adjusted for all the variables in the table.
The figures in bold indicate statistical significance.

stringent definition of diagnostic criteria and large numbers of patients.

TNM classification[16] defines tumors infiltrating the dura of anterior skull base as T4b. Because of the typical location of ITAC in the olfactory cleft, infiltration of the dura is a relatively common occurrence. However, tumor resection, including the anterior skull base, usually ensures a free-margin removal with disease-free margins, as supported by our observations. In fact, only 14 of 43 (32%) pT4b ITACs had positive surgical margins.

The pattern of relapse in our series confirms that local recurrence is the most frequent cause of treatment failure

TABLE 5. Correlation between demographic and clinicopathologic features and complications.

	Any complications			
Variables	No No. of patients (%)*	Yes No. of patients (%)*	Total	*p* value
Sex				
Male	14 (77.8)	4 (22.2)	18	NS
Female	127 (84.1)	24 (15.9)	151	
Age, y				
<60	33 (86.8)	5 (13.2)	38	NS
60–69	39 (84.8)	7 (15.2)	46	
≥70	61 (80.3)	15 (19.7)	76	
pT classification				
T1–T2	71 (86.6)	11 (13.4)	82	NS
T3–T4a	38 (88.4)	5 (11.6)	43	
T4b	31 (72.1)	12 (27.9)	43	
Grade				
1	18 (85.7)	3 (14.3)	21	NS
2	92 (84.4)	17 (15.6)	109	
3	28 (77.8)	8 (22.2)	36	
Dural involvement				
No	118 (86.1)	19 (13.9)	137	**.041**
Yes	22 (71.0)	9 (29.0)	31	
Brain involvement				
No	134 (84.3)	25 (15.7)	159	NS
Yes	7 (70.0)	3 (30.0)	10	
Surgical approach				
Endoscopic resection	35 (92.1)	3 (7.9)	38	**< .001**
ERTC	91 (88.3)	12 (11.7)	103	
Cranioendoscopic resection	15 (53.6)	13 (46.4)	28	
Adjuvant RT				
No	61 (87.1)	9 (12.9)	70	NS
Yes	80 (80.8)	19 (19.2)	99	

Abbreviations: NS, not statistically significant $p > .5$; ERTC, endoscopic resection with transnasal craniectomy; RT, radiotherapy.
Row percentage, Fisher's test, chi-square test for linear trend.
The figures in bold indicate statistical significance.

in ITAC. However, leptomeningeal spread, that was invariably associated with dismal prognosis, occurred in 9 patients (5.4%). Although there are several case reports confirming the potential of ethmoid adenocarcinoma to involve leptomeninges,[21–27] this event has received little attention. Interestingly, tumor spread to leptomeninges can be present even at diagnosis,[21–23] meaning that it is not always necessarily related to surgical manipulation, and seems to be more frequently associated with high-grade lesions. These observations suggest that prophylactic brain irradiation could be considered in high-grade lesions with intracranial invasion.

The main advantages of endoscopic surgery over external techniques are the possibility to thoroughly define the area of insertion and the extent of the lesion, the avoidance of brain retraction when an intradural resection is needed, the absence of external scars, and limited morbidity. In fact, data from an international collaborative study on anterior craniofacial resection clearly showed that, even in expert hands, the procedure is associated with non-negligible mortality (4.7%) and morbidity (36.3%).[17] Conversely, no mortality was observed in either our series or other large series[5,12] of ethmoid adenocarcinoma in which endoscopic surgery was used. Furthermore, complications occurred in 17.1% of our patients. CSF leak, which was the most commonly observed adverse event (4.7%), was successfully managed by revision surgery or positioning of lumbar drainage. Statistical analysis showed that the highest risk of complications was associated with cranioendoscopic resection, which was the most extensive surgical procedure.

In spite of the limitations inherent to any retrospective study, our analysis of a large series of patients treated with a uniform treatment policy supports a definitive paradigm shift in the management of ITAC toward a schedule, including endoscopic surgery in place of external techniques, which have a role only in a minority of patients. Further refinements in the treatment of ITAC could be achieved by studies addressing the possibility to minimize the indications of RT in early-stage lesions, and exploiting the efficacy of new chemotherapeutic or targeted agents based on a better knowledge of the biological profile of the tumor.

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