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Ethmoid Adenocarcinoma—From Craniofacial to Endoscopic Resections: A Single-Institution Experience over 25 Years

Piero Nicolai, MD[1], Andrea Bolzoni Villaret, MD[1], Marco Bottazzoli, MD[1], Emanuela Rossi, PhD[2], and Maria Grazia Valsecchi, PhD[2]

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Abstract

Objectives. To identify factors that influence hospitalization time, complications, and prognosis of patients with ethmoid adenocarcinoma treated with different surgical techniques.

Design. Single-institution retrospective review.

Setting. Academic tertiary care center.

Patients. Sixty-seven patients with ethmoid adenocarcinoma treated from January 1985 to August 2009 were retrospectively evaluated. Surgical treatment included endoscopic resection (n = 12), endoscopic resection with transnasal craniectomy (n = 17), cranioendoscopic resection (n = 9), external approaches limited to the ethmoid (n = 11), and craniofacial resection (n = 18).

Main Outcome Measures. A Cox model was adopted to relate time to death to previous treatment, pT category, grade, and surgical technique. The impact of the same variables on hospitalization time and risk of complications was assessed by linear regression and logistic regression, respectively.

Results. The risk of complications increased for pT4a-b lesions (P = .02) and craniofacial resection (P = .01). Hospitalization time increased by 6.3 days for cranioendoscopic resection (P = .03) and by 11.7 days for craniofacial resection (P < .001). Three- and 5-year overall survivals were 68.0% (standard error = 5.8%) and 48.4% (standard error = 6.9%). Three-year survival was 76.62% and 51.81% for previously untreated and treated patients, respectively, and it was 92.98% and 33.33% in patients treated with endoscopic techniques and craniofacial resection, respectively. Multivariate analysis showed that previous treatment (hazard ratio of death = 3.9, P = .01) and craniofacial resection (HR = 5.16, P = .05) were mainly associated with survival.

Conclusions. Endoscopic techniques, in properly selected patients, were associated with a favorable oncologic outcome and a statistically significant reduction in both complication rate and hospitalization time. This study supports the role of endoscopic techniques in surgical treatment of ethmoid adenocarcinoma.

Keywords

adenocarcinoma, ethmoid, skull base, endoscopic surgery, sinus surgery, craniofacial resection, endoscopic transnasal craniectomy

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Malignant sinonasal neoplasms are rare pathologies, accounting for fewer than 1% of all head and neck cancers.[1] Moreover, for the fact that early symptoms mimic those of rhinosinusitis, they are usually diagnosed at an advanced stage. Other features of sinonasal malignancies are their histologic heterogeneity and the variable geographical distribution of histologies. In some European countries, adenocarcinoma (ADC) is one of the most frequent sinonasal malignancies and typically occurs in woodworkers and leather workers. Greater exposure to hardwood dusts and the incomplete adoption of appropriate safety measures compared with North America can be hypothesized as causes.[2,3]

Treatment of ethmoid ADC is based on surgery, traditionally performed through transfacial approaches or anterior craniofacial resection (CFR), combined in advanced stage lesions with adjuvant radiotherapy (RT). During the past 15 years, transnasal endoscopic surgery has been extensively used to manage small/intermediate ethmoid ADCs.[4,5] More recently, the possibility to

[1]Department of Otorhinolaryngology, University of Brescia, Brescia, Italy
[2]Department of Clinical Medicine and Prevention, University of Milan-Bicocca, Milan, Italy

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Corresponding Author:
Andrea Bolzoni Villaret, MD, Department of Otorhinolaryngology, University of Brescia, Piazza Spedali Civili 1, 25123, Brescia, Italy
Email: dr.bolton@libero.it

achieve endoscopic resection of the anterior skull base (ASB) and overlying dura, with subsequent repair of the defects,[6,7] has further advanced the adoption of endoscopy.

The aim of this study was to review the experience in the management of ethmoid ADC during a 25-year period at a single institution, with special emphasis on the evolution of surgical strategies toward minimally invasive approaches, in order to identify factors affecting the rate of complications, hospitalization time, and prognosis.

Methods

Data on patients affected by ethmoid ADC who underwent surgical resection with curative intent at the Department of Otorhinolaryngology at the University of Brescia and followed for at least 12 months were retrospectively retrieved from a dedicated database. Information on age, gender, work-related exposures, smoking and alcohol habits, tumor histologic variants and degree of differentiation, presentation (previously untreated vs treated), surgical approach, pT category, complications, adjuvant therapy, detection of recurrence/persistence, retreatment, and outcome was reviewed.

Approval was obtained from the hospital committee.

All tumors were restaged according to the 2010 classification of the American Joint Committee on Cancer Staging System (7th ed).[8] Histopathologic slides were reviewed, and tumors were classified according to the World Health Organization (2005)[1] nomenclature in intestinal-type adenocarcinoma (ITAC) and non-ITAC. The degree of differentiation was also reassessed. Signet-ring cell ADCs, although commonly included among poorly differentiated lesions, were analyzed as a separate entity.

Evolution of Surgical Techniques

In the mid-1980s, lesions limited to the ethmoid box were managed by external approaches such as lateral rhinotomy or midfacial degloving. When the lesion reached the ASB or frankly involved the intracranial content, we performed a CFR. In case of tumor growth through the periorbita, clearance of the orbit (CO) was planned. Beginning in the mid-1990s, T1-T2 lesions not encroaching on the ASB began to be managed by endoscopic resection (ER). In the late 1990s, cranioendoscopic resection (CER), which combines an endoscopic approach with a subfrontal craniotomy, was adopted. In the early 2000s, the indications for endoscopic surgery were extended to include lesions in contact with the ASB requiring limited dural resection. Our experience progressively grew, leading us to extend the indications of purely endoscopic techniques to malignancies focally involving the dura and requiring extended meningeal resection. This extended endoscopic procedure, defined as ER with transnasal craniectomy (ERTC), was performed with neurosurgeons. Endoscopic surgical techniques have been already described in previous pubblications.[4,7]

Statistical Methods

Demographic and clinical features were described by using frequencies and percentages. A descriptive analysis was made evaluating associations among demographic and clinical features, twice at time, and calculating the exact Fisher test.

The cumulative probability of death was estimated according to Kaplan-Meier with Greenwood standard error (SE), and comparison of mortality between different subgroups was performed using log-rank test in univariate analyses.

The Cox regression model was used to investigate factors that independently affected the overall hazard of death. The model was run on the entire cohort considering as regressors the variables previous treatment, pT category, grade, and surgical technique. The assumption of proportional hazards was assessed by graphic check on the log-cumulative hazard for each covariate, and major departures were not detected. Results of the Cox model were expressed in terms of estimated hazard ratio (HR) and 95% confidence interval (CI).

Complications were analyzed by using a logistic regression model with the same regressors as in previous analyses. Results were expressed in terms of odds ratio and 95% CI.

Hospitalization time was analyzed by using a linear regression model with the same regressors considered in the analysis of complications. Results were expressed in terms of estimated linear regression coefficients and 95% CI.

P values were considered significant when $\leq .05$. All computations were carried out using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Results

A total of 67 patients, treated from January 1985 to July 2009, were included. Some of them have been included in previous reports.[4] Epidemiologic, histopathologic, and clinical findings are summarized in **Table 1**. Median age was 67 years (range, 34-86 years; interquartile range, 58.5-72.0 years; peak of incidence, seventh to eighth decade).

Only 2 (2.99%) patients presented with neck metastasis staged as pT4bN2b and pT4bN2c, respectively; both patients had a signet-ring cell ADC.

Overall, 40 (59.70%) patients reported complications in the postoperative course. Twelve (17.91%) developed major complications such as severe pneumocephalus (3; 4.48%), stroke (2; 2.99%), cerebrospinal fluid (CSF) leak (2; 2.99%), meningitis (1; 1.49%), sepsis (1; 1.49%), brain abscess (1; 1.49%), and severe epistaxis (1; 1.49%). One (1.49%) patient died because of surgery; he underwent a CFR for a pT4bN0M0 G3 ADC. Residual 28 patients had minor complications, non-life-threatening and not requiring surgical revision, such as pneumocephalus, agitation, minor subdural blood collection, central venous catheter infection, fever of unknown origin, deep venous thrombosis, epilepsy, major headache, pneumonia, hallucinations, VI CN palsy, anisocoria, and epiphora. The distribution of complications in relation to the surgical approach (**Figure 1**) was the following: 1 (1/12, 8.33%) for ER, 8 (8 /17, 47.05%) for ERTC, 5 (5/11, 45.45%) for external approaches, 9 (9/9, 100%) for CER, and 17 (17/18, 94.44%) for CFR.

Overall, 34 (50.75%) patients received some form of adjuvant treatment (**Table 1**).

Recurrences or persistences were observed in 26 (38.81%) and 4 (5.97%) patients, respectively. Recurrences occurred in

Table 1. Demographic Data, Histopathologic Findings, and Clinical Information of the Present Series

		No. of Patients	Percentage
Gender	Male	63	94.03
	Female	4	5.97
Work-related exposure	Wood dusts	39	58.21
	Wood and leather dusts	2	2.99
	Leather dusts	17	25.37
	Other exposures	5	7.46
	No exposure	4	5.97
Smoking habit	Nonsmoker	25	37.31
	Former smoker	29	43.28
	Smoker	9	13.43
Alcohol habit	Alcohol social user	39	58.21
	Alcohol abuser	28	41.79
Presentation	New primary	44	65.67
	Recurrence	19	28.36
	Persistence	4	5.97
Histologic variants	Intestinal-type ADC	64	95.52
	Non–intestinal-type ADC	3	4.48
Grade	G1	9	13.43
	G2	30	44.78
	G3	20	29.85
	Ring cells	8	11.94
Surgical technique	ER	12	17.91
	ERTC	17	25.37
	CER	9	13.44
	CFR	14	20.90
	CFR + CO	4	5.97
	External approach	11	16.41
Complications	No complications	27	40.30
	Minor complications	28	41.79
	Major complications	12	17.91
pT category	T1	8	11.94
	T2	16	23.88
	T3	4	5.97
	T4a	14	20.90
	T4b	25	37.31
Adjuvant treatment	None	33	49.25
	RT	30	44.78
	RT + CHT	2	2.99
	CHT	1	1.49
Recurrences	None	37	55.22
	Recurrence	26	38.81
	Persistence	4	5.97
Follow-up status	NED	31	46.27
	AWD	2	2.99
	DOC	11	16.42
	DOD	23	34.33

Abbreviations: ADC, adenocarcinoma; AWD, alive with disease; CER, cranioendoscopic resection; CFR, craniofacial resection; CHT, chemotherapy; CO, clearance of the orbit; DOC, dead of other causes; DOD, dead of disease; ER, endoscopic resection; ERTC, endoscopic resection with transnasal craniectomy; External approach, exclusive external approaches other than CFR; NED, no evidence of disease; RT, radiotherapy.

18 patients at the primary site, in 1 in the neck, in 6 at distant sites, and in 1 both at primary and distant sites: 19 died of disease (DOD), 2 are alive with disease (AWD), 4 underwent successful salvage treatment (all on the site of primary: 2 underwent ER and 2 CFR), and 1 died of meningitis 10 years after surgery. None of the patients with persistent disease could be rescued.

Median follow-up was 80 months (range, 12-282 months). At the time of last follow-up, 31 (46.27%) patients had no evidence of disease (NED), 23 (34.33%) DOD, 11 (16.42%)

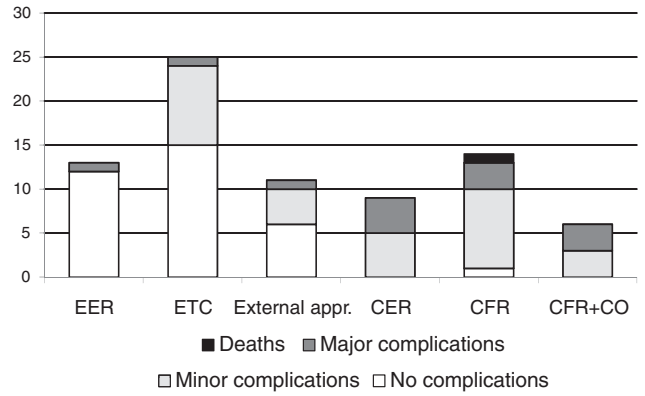

Figure 1. Distribution of complications in relation to the approach adopted. $P < .001$. CER indicates cranioendoscopic resection; CFR, craniofacial resection; CO, clearance of the orbit; ER, endoscopic resection; ERTC, endoscopic resection with transnasal craniectomy; External appr., exclusive external approaches other than CFR.

died of other causes (DOC), and 2 were AWD. The 3- and 5-year overall survivals were 68.0% (SE = 5.8%) and 48.4% (SE = 6.9%), respectively.

Univariate Analysis

No significant association was found at the univariate analysis between different kinds of work-related exposures and histopathologic variants ($P = .30$) or between years of exposure and histopathologic variants ($P = .64$). Grade was associated with patient age (in decades) ($P < .05$); indeed, we noticed that 7 of the 8 patients with a signet-ring cell ADC were 60 to 69 years of age. The pT category was associated with the grade ($P = .03$); in particular, all the 8 pT1 were G1-G2; only 4 of the 20 G3 were pT2, whereas the others were pT4a-b. Moreover, half of the 8 signet-ring cell ADCs were pT4b. On the other hand, pT category was not associated with work-related exposures ($P = .31$), years of exposure ($P = .14$), or histopathologic variants ($P = .76$).

The surgical technique was associated with pT category of the primary ($P < .001$) (**Table 2**). In fact, the majority of pT1-2 lesions (22/24; 91.67%) were treated by pure endoscopic procedures (ER, ERTC) or by external approaches not including resection of the ASB. In contrast, advanced staged lesions ($pT \geq 3$) were treated in 24 (24/43; 55.81%) cases with CER or CFR±CO and in 6 (6/43; 13.95%) cases—all pT4a—with external approaches not requiring dural resection. These procedures were performed when ER and ERTC were not yet available.

No statistically significant relation was reported between surgical approach and previous treatment ($P = .06$), even though 91.67% of ERs (11/12) and 76.47% of ERTCs (13/17) were performed on previously untreated patients.

Complications were significantly related to the surgical technique (**Figure 1**) ($P < .001$) and to pT category ($P < .001$).

In particular, all patients except 1 (26/27; 96.30%) receiving some form of craniotomy (CER, CFR±CO) developed at least 1 complication. Nine of 29 (31.03%) patients who underwent endoscopic procedures (ER, ERTC) developed complications (**Figure 1**).

According to pT category, no patients with pT1 lesions experienced complications, whereas all major complications were observed in pT4 patients (2 pT4a, 10 pT4b).

Adding adjuvant therapy was related to pT category ($P = .02$). No patient with a pT1 lesion received adjuvant therapy. No significant relation was observed between adjuvant therapy and grade ($P = .05$), although 7 of 8 patients with a signet-ring cell ADC underwent adjuvant therapy.

The hospitalization time (interquartile range, 7.0-17.75 days) was significantly related to pT category ($P < .001$) and surgical technique ($P < .001$). In 1 case only, the hospitalization time was prolonged until 124 days because of surgical treatment of a second primary abdominal tumor. As an outlier of the present series, the patient was not considered in the analysis of the hospitalization time.

Development of recurrence was associated with surgical technique ($P < .001$): all the CFR+CO persisted or recurred, 8 of 14 CFR recurred and 7 of 9 CER persisted or recurred, whereas only 3 of 17 ERTCs recurred, as only 2 of 12 ERs. No significant relationship was observed between development of recurrence and exposures ($P = .13$), pT category ($P = .06$), or grade ($P = .07$). All patients with persistence were staged pT4b, and most of the recurrences (20/26; 76.92%) were staged pT4a-b. Of the 8 signet-ring cell ADCs, 6 recurred and 1 persisted.

Follow-up status was not associated with either previous treatment ($P = .26$), or grade ($P = .21$). Follow-up status was related to pT category ($P < .01$): 14 (14/23; 60.87%) patients DOD were pT4b, 7 (7/23; 30.43%) were pT4a, 1 (1/23; 4.35%) was pT3, and 1 (1/23; 4.35%) was pT2. Two patients AWD

Table 2. Surgical Approach by pT Category ($P < .001$)

	ER	ERTC	CER	CFR	CFR + CO	External Approaches	Total
pT1	3	4	0	0	0	1	8
pT2	6	4	2	1	0	4	16
pT3	2	3	0	1	0	0	4
pT4a	2	3	2	1	0	6	14
pT4b	0	4	6	11	4	0	25
Total	12	17	9	14	4	11	67

Abbreviations: CER, cranioendoscopic resection; CFR, craniofacial resection; CO, clearance of the orbit; ER, endoscopic resection; ERTC, endoscopic resection with transnasal craniectomy; External approaches, exclusive external approaches other than CFR.

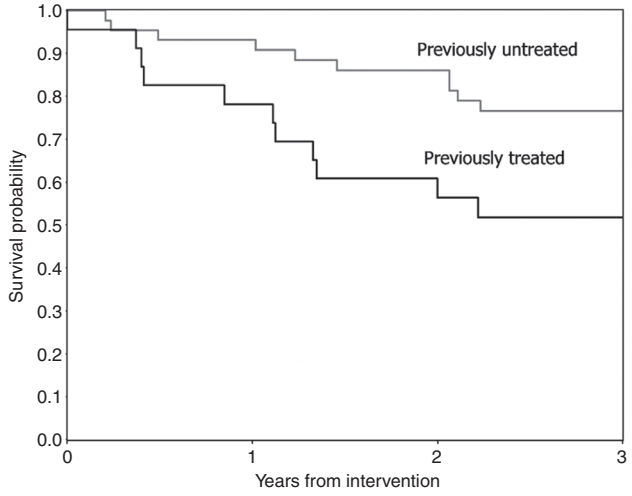

Figure 2. Kaplan-Meier analysis for survival of previously treated versus untreated patients (P = .04).

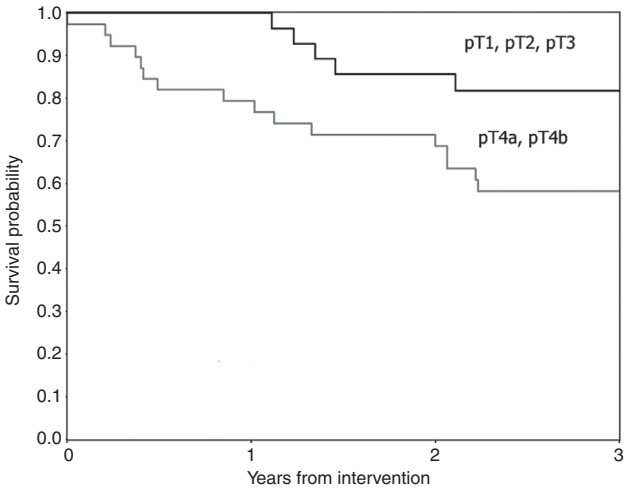

Figure 3. Kaplan-Meier analysis of patient survival according to pT category (up to pT3 vs pT4a-b) (P < .01).

were both pT4b. A significant association was observed between follow-up status and the surgical technique (P < .001): the patients AWD underwent CER and CFR; all 4 patients who underwent CFR+CO died of disease. Development of recurrences was strongly related to follow-up status (P < .001): all the 4 patients with persistent disease were DOD and most of the patients who developed a recurrence were DOD (19/26) or AWD (2/26).

Kaplan-Meier analysis highlighted a significant difference between previously treated and untreated patients: 3-year survival was 51.81% (SE = 10.5%) and 76.62% (SE = 6.5%), respectively (P = .04) (**Figure 2**).

A significant difference was observed comparing patients with lesions up to pT3 (81.8%, SE = 7.4%) versus patients staged pT4a-b (58.3%, SE = 8.0%) (P < .01) (**Figure 3**).

Three-year survival according to surgical techniques adopted was 92.98% (SE = 4.8%) for ER and ERTC, 66.67%

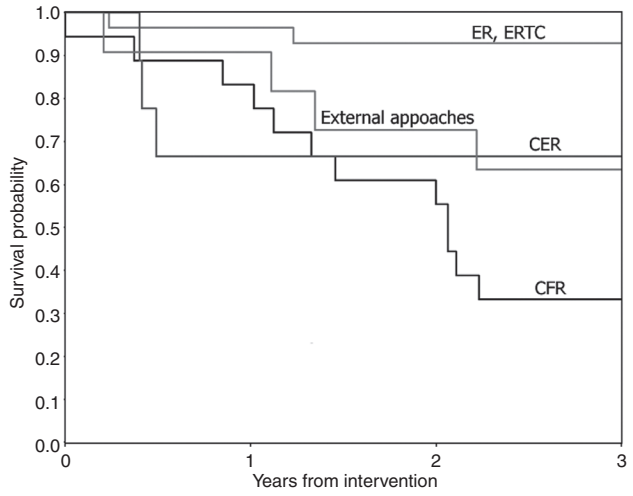

Figure 4. Kaplan-Meier analysis of patient survival according to the surgical technique adopted (P = .01). CER indicates cranioendoscopic resection; CFR, craniofacial resection, with or without clearance of the orbit); ER, endoscopic resection, ERTC, endoscopic resection with transnasal craniectomy; External approaches, exclusive external approaches other than CFR.

(SE = 15.71%) for CER, 63.64% (SE = 14.5%) for external approaches, and 33.33% (SE = 11.11%) for CFR±CO, respectively (**Figure 4**): the curves were significantly different (P = .01).

Multivariate Analysis

Complications were modeled on previous treatment, grade (G1 vs G2, G3, signet-ring cells), pT category (pT ≤ 3 vs pT4a-b), and surgical techniques (ER-ERTC vs CER, CFR, external approaches). This model revealed that pT4a-b lesions were related to a risk of complications that was 5-fold the risk of patients with lower pT category; the surgical approach was also related to a higher risk of complications (P = .01). In particular, the risk of complications related to CFR was 20.72 times higher than ER-ERTC (**Table 3**).

Hospitalization time was modeled on grade (G1 vs G2, G3, ring cells), pT category (pT ≤ 3 vs pT4a-b), and surgical techniques (ER-ERTC vs CER, CFR, external approaches). Hospitalization time significantly increased according to surgical technique (P < .001): CER and CFR increased the hospitalization time by 6.3 and 11.7 days on average; no other parameter had a significant influence (**Table 4**).

Risk of death was regressed on previous treatment, grade (G1 vs G2, G3, signet-ring cells), pT category (pT ≤ 3 vs pT4a-b), and surgical technique (ER-ERTC vs external approaches, CER, CFR). Previously treated patients had a significantly higher risk of death than patients not previously treated (HR = 2.42, P = .03). The surgical approach was statistically significant (P = .05) with an HR of death of 5.16, 4.04, and 3.34 for CFR, CER, and external approaches respectively (**Table 5**).

Comment

ADC is a rare tumor of the sinonasal tract, prevalently occurring in the ethmoid. Specific information on epidemiology,

Table 3. Multivariate Analysis on 67 Patients Evaluating the Impact of Prognostic Factors on Complication Onset

	Odds Ratio	Confidence Interval (95%)	*P* Value
Previous treatment	0.776	0.154 to 3.904	.758
G2	14.778	1.263 to 21.553	.154
G3	13.224	0.642 to 340.014	
Signet-ring cells	28.155	0.541 to 323.319	
pT4a + pT4b	5.217	0.591 to 14.427	.022
CER + ext appr	2.920	0.792 to >999.999	.011
CFR ± CO	20.721	1.838 to 233.659	

Abbreviations: CER, cranioendoscopic resection; CFR, craniofacial resection; CO, clearance of the orbit; ext appr, exclusive external approaches other than CFR.

Table 4. Multivariate Analysis on 66 Patients Evaluating the Impact of Prognostic Factors on Hospitalization Time

	Regression Coefficient	Confidence Interval (95%)	*P* Value
Previous treatment	2.620	−0.951 to 6.191	.147
G2	3.621	−1.217 to 8.459	.312
G3	3.332	−2.077 to 8.741	
Ring cells	2.352	−3.935 to 8.639	
pT4a + pT4b	2.094	−1.612 to 5.799	.263
Ext appr	−0.388	−0.806 to 4.315	<.001
CER	6.272	0.806 to 11.738	
CFR ± CO	11.726	7.330 to 16.123	

Abbreviations: CER, cranioendoscopic resection; CFR, craniofacial resection; CO, clearance of the orbit; Ext appr, exclusive external approaches other than CFR.

biological behavior, and treatment outcome is difficult to collect from the literature, because most articles have grouped together tumors with different sites of origin and histologies without performing a subgroup analysis. Only a few articles have specifically focused on ethmoid ADC.[3,5,9-12] However, additional data can be obtained from reports analyzing the efficacy of specific treatments, such as CFR[13,14] or endoscopic surgery.[15] Another source of bias is the lack of homogeneity in histological classification and terminology. ADCs are divided in ITACs and non-ITACs.[1] The former, by far the most frequent in the ethmoid, are further classified into well-, moderately, and poorly differentiated and are associated with exposure to organic dusts, especially wood and leather. No strong evidence for minor risk factors as farming, brick working, truck driving, and fishing has been reported.

Patients usually present with persistent unilateral nasal obstruction, rhinorrhea, or recurrent epistaxis. Lymph node or distant metastases are uncommon events reported in up to 10%[9] and 20%[16] of cases. In our series, 2 (2.99%) patients, both signet-ring cell patients, had nodal disease at diagnosis, and 2 (2.99%) additional cases developed during follow-up; distant metastases were observed in 7 (10.45%) cases.

Table 5. Multivariate Analysis on 67 Patients Evaluating the Impact of Prognostic Factors on Overall Mortality (34 Events)

	HR	HR Confidence Interval (95%)	*P* Value
Previous treatment	2.422	1.08-5.43	.032
G2	1.016	0.2-5.169	.113
G3	2.339	0.444-12.315	
Signet-ring cells	3.346	0.566-19.787	
pT4a + pT4b	1.447	0.53-3.945	.471
CFR ± CO	5.155	1.434-18.536	.050
CER	4.036	0.965-16.887	
Ext appr	3.335	0.958-11.612	

Abbreviations: CER, cranioendoscopic resection; CFR, craniofacial resection; CO, clearance of the orbit; Ext appr, exclusive external approaches other than CFR.

The mainstay of treatment for ethmoid ADC is surgery, and CFR has been considered for many years the standard for lesions in close vicinity to or extending through the ASB.[3,14,17] This approach is strongly recommended by those who believe that en bloc resection is mandatory and who consider endoscopic approaches inadequate, because they obtain a simple piecemeal removal. This criticism does not consider that ER and ERTC are performed through a systematic tumor disassembling, which allows the surgeon to tailor the resection according to intraoperative findings and to clearly identify tumor origin, which is often surprisingly limited.[18]

A specific issue with ADC is the extent of ethmoid resection. Some authors limit the resection to the involved site,[5] although this exposes patients to the risk of developing not only recurrences but also second primaries in the residual ethmoid. This concept has been emphasized by Cantù et al,[3] who recommended resecting the entire ethmoid box in view of the observation of preneoplastic and neoplastic foci in macroscopically uninvolved ethmoid areas. This applies in particular to ITAC, where the whole ethmoid mucosa has been exposed to carcinogenetic dusts. Although at the beginning of our experience in endoscopic surgery, resection was limited to the involved site, during more recent years we routinely perform a complete ethmoidectomy.

The role of RT is controversial. Traditionally, it has been stated that postoperative RT at the primary site increases the likelihood of local control. In agreement with recent recommendations,[19,20] during the past years we have limited the indications for RT to patients with advanced lesions or positive margins. However, the validity of this policy needs to be confirmed.

Complication rates in our series significantly varied in relation to surgical techniques. The prevalence of complications in endoscopic resections, which ranged from 8.33% (ER) to 47.6% (ERTC), was in accordance with previously reported data (14.5%-47%),[7,21-23] with no case of infectious intracranial complication or fatality. In contrast, a 94.44% complication rate was observed in CFR±CO, a value higher than in other reported series (30%-54%).[14,24] This can be explained by the fact that

this approach was reserved for advanced lesions (83.33% were pT4b) and that even minor complications were carefully collected: only 22.22% of cases had major complications.

Mortality, meningitis, and CSF leak rates in CFR (5.56%, 0%, and 1.49%, respectively) were otherwise comparable with those reported, ranging from <2%[14] to 7.6%,[13,14,24] <1%[14] to 9%,[25,26] and <1%[27] to 16%,[25] respectively. The risk of complications was increased (about 20 times) in CFR and was independent of any other variable (**Table 3**).

To the best of our knowledge, no other published studies performed a multivariate analysis on hospitalization time, although some reports have suggested that endoscopic procedures are associated with more limited hospitalization.[28] The Cox model on hospitalization time demonstrated that only surgical technique had a statistical relevance.

The comparative analysis of data from the literature on ADC survival is hindered by many factors: variability of treatment and distribution in relation to pT category, limited series, and different methods in evaluating survival. We chose to focus on overall survival, because the cause specific cumulative incidence (also called "disease-specific survival"), which considers alive patients DOC, is not a true survival. Additionally, overall survival is more frequently reported in ADC literature. Our finding of a 48.4% 5-year overall survival is within the range (44.8%-60%)[5,9,13,29,30] reported in the literature.

Surgical technique maintained its statistical significance in multivariate analysis ($P = .05$): patients treated with CFR, CER, and external approaches had a 5-, 4-, and 3-fold higher risk of death than endoscopically treated patients, respectively (**Table 5**). Furthermore, the Kaplan-Meier analysis of survival in relation to the surgical technique showed a dramatic improvement in 3-year survival for ER-ERTC (**Figure 4**). These results might be influenced by the selection given the inclusion criteria adopted for endoscopic surgery. In some articles, survival of patients undergoing a purely endoscopic approach was even higher, but the number of cases reported was limited or tumors were mostly low stage.

The major strengths of our study lie in the fact that our population included only ethmoid ADC and that the multivariate analyses addressed not only survival but also the risk of complications and hospitalization time. As major limitations, data were retrospectively collected over a 25-year period, and although the median follow-up was 80 months, 13.43% of patients had fewer than 3 years of observation.

In conclusion, although ethmoid ADC shows better survival compared with other histologies, it must be considered an aggressive disease requiring resection with wide margins. Increasing evidence in the literature supports the use of endoscopic techniques, which in our experience are associated with favorable survival, decreased hospitalization time, and reduction of complications in comparison with CFR. Because the rarity of the disease does not allow comparative studies, which would not even be ethically justified in view of the data already supporting the validity of endoscopic approaches, data on large cohorts of patients should be collected on specific histologies on a multi-institutional basis to further refine treatment strategies.

Author Contributions

Piero Nicolai, major contribution in critical revision of the paper for important intellectual content, contribution to conception and design of the study, final approval; **Andrea Bolzoni Villaret**, major contribution in drafting the article and to its conception and design, major contribution to interpretation of the data, final approval; **Marco Bottazzoli**, major contribution in data collection, contribution in article revising, final approval; **Emanuela Rossi**, major contribution in statistical analysis of data and their interpretation, contribution in revision of the article, final approval; **Maria Grazia Valsecchi**, major contribution in statistical analysis of data, minor contribution in revision of the article, final approval.

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