Treatment of sinonasal adenocarcinoma: a population-based prospective cohort-study

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Abstract

Objectives: Sinonasal adenocarcinoma (AC) is a potentially curable disease, despite being an aggressive malignancy. Long-term survival can be achieved with early diagnosis and adequate multidisciplinary treatment. Our goal was to evaluate outcomes for patients with AC treated at our institution.

Design: In a population-based consecutive prospective cohort, we conducted an analysis of all patients treated for surface epithelial AC between 1995 and 2018.

Results: 20 patients were included and follow-up was 100%. The mean follow-up time was 89 months for the entire cohort (112 months of patients with no evidence of disease). Intestinal type AC was found in 65%, and non-intestinal type AC in 35% of all cases. 75% had stage T3/4 disease. Tumor grade was intermediate/high in 65%. 18 patients underwent treatment with curative intent (craniofacial resection (CFR) in 61%, transfacial approach in 39%, followed by adjuvant radiotherapy in 89%), achieving negative margins in 56% of cases. Overall survival was 90%, 68%, and 54% after 2, 5, and 10 years of follow-up. Corresponding disease specific survival was 90%, 73%, and 58%. Age over 60 years, tumor with maxillary origin, and microscopic bone invasion were negative prognostic factors. Radical CFR was correlated to better OS and DSS.

Conclusion: The high probability of achieving radicality with CFR, the low complication rate, the acceptable toxicity of modern irradiation modalities, and these promising survival rates indicate that this strategy might be considered safe and effective option for treating patients with very advanced sinonasal AC.

Keywords: sinonasal adenocarcinoma, craniofacial resection, adjuvant radiotherapy, survival

Introduction

Sinonasal carcinomas are uncommon neoplasms that account for approximately 3% to 5% of all upper respiratory tract malignancies.[1-3] Adenocarcinoma (AC) represents the third most common malignancy in the sinonasal tract, after squamous cell carcinoma (SCC) and adenoid cystic carcinoma (AdCC), and account for approximately 15% of all sinonasal cancers.[1]

ACs affect predominantly male patients and occur most frequently in the ethmoid sinuses, but can also originate in other sites of the nasal cavity (maxillary sinus in <10%).[4-6] It has been hypothesized that this distribution may reflect the deposition of carcinogens in the middle meatus. However, it has been suggested, based on endoscopic findings, that many, if not all, adenocarcinomas arise in the olfactory cleft.[7]

Primary adenocarcinomas of the sinonasal tract may originate from respiratory surface epithelium or the underlying seromucinous glands, and are divided into two main types; s*alivary type* AC and *non-salivary type* AC (Figure 1). The *salivary-type AC* arise from the sero-mucinous glands and surface epithelium of the nasal cavity and paranasal sinuses. They comprise 5-10% of sinonasal ACs, and are usually well-defined myoepithelial neoplasms, which closely resemble their salivary counterparts. AdCC is the most common salivary-type carcinoma, and the second most common sinonasal malignancy overall after SCCs, and it represents 10–18 % of all sinonasal malignancies.[6, 8, 9] The 5-year survival rates range from 40% to 60% in the literature, with poorest results in AdCC (6, 8, 10).

The non-salivary-type – also called surface epithelial - is further separated into intestinal (ITAC) and non-intestinal subtypes (NITAC).[6, 11-13] ITAC is the second most common type of sinonasal AC after AdCC and is generally aggressive with a local recurrence rate of up to 50%, lymphatic spread in 10%, and a distant metastasis rate of 20%.[5] Tumors in this group resemble intestinal epithelium and often arise in the ethmoid sinus. They are aggressive malignancies, and may spread to adjacent structures including the orbit, the pterygopalatine fossa, the infratemporal fossa and the cranial cavity.[6] ITACs are further subdivided into five categories according to Barnes: papillary, colonic, solid, mucinous, and mixed types.[11] The histologic subtypes have been found to correlate with clinical behavior: e.g. well differentiated papillary ITACs have an indolent course, but patients with solid and mucinous ITACs have an untoward outcome.[11, 12, 14] A remarkable association has been identified between long-term exposure to wood dust and the occurrence of ITAC; workers with occupational exposure to

hardwood dusts may show incidences 1000 times those of the general population.[15-18] This kind of exposure has been observed in ca. 20% of reported cases.[18, 19] Also, occupational exposure to dusts in the shoe and leather industry.[20] and in textile manufacture, as well as to chromium and nickel, have been suspected. The carcinogenic compounds have not been identified, but a possible etiologic role for tannins has been discussed.[14]

NITAC are of presumed seromucous gland origin, have marked morphologic heterogeneity, they can arise anywhere in the sinonasal tract, and are divided in high-grade and low-grade types.[13] High-grade NITACs are rare malignancies of the sinonasal tract and are frequently found in the maxillary sinus. These tumors have heterogeneous features which may overlap with those of other malignancies of this area, often leading to difficulties during histopathological diagnosis. High-grade NITACs have a very poor prognosis with 3-year survival rates of approximately 30%.[1, 5, 6, 21]

Low-grade NITACs are uncommon (approximately 13% of sinonasal AC) and occur mostly in the ethmoid sinus, the nasal cavity, and the maxillary sinuses.[6] These carcinomas have no known association with environmental carcinogens. The disease is usually localized, but local recurrences are possible. Metastasis is unusual, and death of disease is rare. The overall prognosis of the patients is favorable, 5-year survival rates up to 85% are reported in the literature.[5, 6, 22-24]

The paranasal sinuses are anatomically complex and quite "clinically silent", allowing a tumor to grow to a significant size before symptoms and signs develop. Therefore, at the time of diagnosis, most patients present with advanced stage disease and have extensive involvement of adjacent sites, such as the orbit, skull base and the central nervous system, leading to difficulties in the management of AC.[25-30] Many patients with AC of lower stages can be effectively treated with radiotherapy (XRT). However, surgical excision followed by XRT is the favoured choice of treatment worldwide.[5] Open craniofacial resection (CFR) is often warranted in cases of involvement of the cribriform plate or dura mater, and in many cases adjuvant XRT is needed due to the advanced stage of the disease at diagnosis.[31]

There is a scarcity of prospectively collected data addressing management options and treatment outcomes because of the rarity of this disease. The goal of this population-based study was to evaluate the management of

patients with surface epithelial (non-salivary-type) AC treated at Oslo University Hospital in Norway from 1995 to 2018, and to evaluate our results in light of the international literature.

Materials and method

Clinical setting

Oslo University Hospital (OUH) is a tertiary referral, comprehensive cancer centre with a catchment area of approximately 3 million inhabitants (56% of the entire Norwegian population). In addition, our institution accepts referrals from other health regions in Norway.

Patient cohort

Our prospective database for brain tumors and the pathology registry of head and neck cancers were searched to identify patients eligible for this study. Inclusion criteria were histologically verified surface epithelial (non-salivary-type) AC and treatment at OUH between 1995 to date. The medical records of patients were also reviewed retrospectively to identify the study parameters not included in the database records.

Tumor-related variables

A histopathological diagnosis of AC was made by a consultant pathologist at presentation. All cases were formally re-examined by a dedicated head and neck pathologist, re-classified into correct histological subtypes, and evaluated for nerve, vessel and bone invasion. Staging of tumors was based on the TNM staging system of the American Joint Committee on Cancer for a maxillary sinus, or ethmoid sinus/nasal cavity cancers.[32] Tumor size, orbital, dural and/or cerebral infiltration was determined from radiographical images at diagnosis and completed with intraoperative registrations. The quality of the surgical margins was also retrospectively scrutinized.

Treatment variables

According to the tumor specific variables (i.e. tumor size and location, presence or absence of metastases to lymph nodes and/or distant metastasis), and the patient specific variables (i.e. age, general condition, complications and mental condition), a personalized treatment plan was made for each patient after consultation with the multidisciplinary team (MDT) that includes head and neck surgeon, oncologist, neurosurgeon, pathologist, radiologist, and ophthalmologist, if required.

The surgical technique was patient-specific tailored based on the location of the tumor and the proximity to vital structures. In general, for resections with curative intent, gross tumor resections (GTR) were performed in an *en-*

bloc fashion, if possible. In cases of a median or paramedian localization with invasion of the nasal cavity, hard palate and/or maxillary sinus, or primary localization in the medial maxillary sinus or nasal cavity, a lateral rhinotomy (LR), a modified midfacial degloving (MFD), or an endoscopic sinus surgery (ESS) technique was used to provide better visualization.

The Weber-Fergusson incision modified by Zange[33] was used in selected cases to perform total hemimaxillectomy in particularly large tumors. The lamina papyracea was resected for tumors extending to the lateral ethmoidal wall, while the periorbita was resected in cases of invasion. Tumors infiltrating the orbital fat were treated with orbital exenteration. If an invasion of the anterior skull base was suspected, an additional bicoronal approach was done, offering the possibility of a transcranial-transfacial resection of the tumor (i.e. craniofacial resection; CFR). The bony skull base (cribriform plate and fovea ethmoidalis) was resected for tumors involving the bony skull base and dural resections were performed for tumors with skull base erosion. Additional brain tissue from the frontal lobe was resected in cases with limited brain involvement as needed to achieve negative surgical margins.

The reconstruction of the resected tissues was performed according to size and staging. Small defects were closed by local flaps or buccal fat pad, while larger defects were either closed by pedicled temporalis flaps or microvascular flaps. In many cases, an obturator prosthesis was applied to improve patient comfort and to facilitate clinical follow-up of the resection cavity. Closed reconstruction was offered in selected cases, when the risk of recurrence was considered low. Reconstruction of anterior skull base defects was done using a 2-layer closure of the dura and skull base. Duroplasty was performed using avascular grafts, and from 1998 onwards, skull base reconstruction was done using vascularized pericranial flaps.[26] Surgical treatment was deemed adequate if resection margins were negative according to a surgeon and pathologist joint assessment.

Statistical analysis

The main end-points of this study were overall survival (OS) and disease-specific survival (DSS). Follow-up time was calculated from the date of primary treatment to either death, with or without disease, or last known status. Event-time distributions were approximated using the Kaplan-Meier estimator[34] and the log rank test was used to test for any significant differences between the survival curves.[35] Prognostic factors for OS and DSS were identified using the Cox proportional hazards regression model.[36] Whether or not the observed proportions

for a categorical variable differed from the hypothesized proportions was determined using the chi-square test or Fisher's exact test, as appropriate.[37] The level of statistical significance was set at p-value = 0.05. Descriptive statistics were reported as a mean with a 95% confidence interval (CI) or a median with a range, as appropriate. Statistical analysis was conducted using SPSS® version 22 (SPSS Inc., Chicago, USA).

Results

Clinical findings

The medical records and pathological specimens of 25 identified patients were reviewed. Five patients were excluded after histopathology review (AdCC in three, carcinoma ex pleomorphic adenoma in one, and malignant ameloblastoma in one case). Finally, 20 patients were found eligible for this study. The sex distribution showed a clear male predominance with 15 male (75%) and 5 female (25%) patients. All of the patients were of Caucasian descent. Nine (45%) patients had possible occupational hazard present in their history; long-term exposure to hardwood dusts in six, to chromium and nickel in two, and to tannins in one case. The mean age at diagnosis was 57.5 years (range 25-81 years, 95% CI: 50.0-65.1 years). The peak incidence of disease in our cohort occurred in the eighth decade of life. Patient characteristics are summarized in Table 1.

Nasal stenosis was the most common presenting symptom - observed in 65% of all cases - followed by epistaxis, local pain (2 cases each), reduced vision and swelling (1 case each), while a single case was diagnosed due to a distant metastasis originating from the disease. Presenting symptoms were predating primary diagnosis by a mean of 9.4 months (range 1-24, 95% CI: 5.7-13.2).

Tumor characteristics

The tumor originated from the ethmoid sinus in 17 (85%), and from the maxillary sinus in 3 (15%) cases. The mean tumor size was 3.7 cm (a median of 3.8 cm, 95% CI: 3.1-4.4). Orbital involvement was observed in 8 (40%), dural involvement in 5 (25%) and brain invasion in a single (5%) case. Eleven (55%) patients had T4 disease at the time of diagnosis, while 4 (20%) patients had T3, three (15%) had T2 and two (10%) had T1 disease. No patients presented with positive lymph node status, while one patient had distant metastases (M2) at the time of diagnosis.

Histopathology showed ITAC in 13 (65%), low-grade NITAC in 4 (20%), and high-grade NITAC in 3 (15%) cases. The grade of overall tumor differentiation regardless of histopathological subclassification was high in five (25%), intermediate in 8 (40%), and low in 7 (35%) cases. Microscopic bone invasion (lamina cribrosa) was present in 10 (50%), nerve invasion in 5 (25%), and vessel invasion in 3 (15%) cases. Multifocal histology was present in four (20%) cases, remarkably, all of these patients had occupational exposure over time. Tumor characteristics are summarized in Table 1.

Treatment

Treatment details are summarized in Figure 2 and Table 2. Eighteen (90%) patients were selected for surgical treatment with curative intent after multidisciplinary evaluation, while surgery was intentionally omitted in two (10%) patients, due to extensive comorbidity and distant metastases present at the time of diagnosis in one case each. These patients underwent non-surgical oncologic treatment only.

Eleven (61%) patients underwent open CFR, using LR in nine (50%), and MFD in two (11) cases as the transfacial approach. Seven (39%) patients underwent tumor resection using transfacial approach only; LR in 4 (22%), and ESS in 3 (17%) cases.

Negative surgical margins were achieved in 10 (56%) cases. Tumor cells were found in – or close – to the resection margins in 8 (44%) cases.

All patients undergoing surgical resection underwent adjuvant XRT (50-70 Gy) postoperatively, except the two patients presenting with T1 disease. Oncological treatment was administered in accordance with the guidelines of the Danish Head and Neck Cancer Group (DAHANCA).[38, 39]

Complications related directly to surgical treatment were registered in two cases (meningitis, osteonecrosis).

Outcomes

The outcomes of the entire study cohort are summarized in Table 3. We obtained 100% follow-up. The mean follow-up time of the entire cohort was 89 months (range 1–239 months, median 71.9 months, 95% CI: 53.6–123.9) as of June 15st 2018 (date of final follow-up). The mean follow-up time of patients with no evidence of disease was 112 months (range 5–239 months, median 102.8 months, 95% CI: 61–162.5). Importantly, none of the patients were lost to follow-up.

The overall survival (OS) rates in the entire cohort were 90%, 68%, and 54% after 2, 5 and 10 years, respectively. Corresponding disease specific survival rates (DSS) were 90%, 73%, and 58%.

Age at diagnosis over 60 years (*p*-value = 0.004), tumor origin from the maxillary sinus (*p*-value = 0.022), and microscopic bone invasion (*p*-value = 0.041) were associated to significantly dismal outcome.

We found no significant correlations between survival and previous occupational exposure, dural-, orbital-, or brain invasion, tumor size, tumor stage, microscopic nerve- or vessel invasion or multifocal pathology.

Outcomes after treatment with curative intent

Ten (56%) of all 18 patients are still alive in this cohort, while eight patients have deceased, of which whom six due to their disease, and two due to other reasons. All patients who underwent surgical treatment with negative margins (n=10) were alive with no evidence of the disease (NED) at final follow-up. The longest follow-up time was 20 years. In contrast, six out of eight patients with positive surgical margins were deceased due to their disease (DOD), while two patients are still alive with NED (after 127 and 157 months of follow-up, respectively).

The OS rates were 94% at two years, 76% at five years, and 61% at 10 years of follow-up. The corresponding disease-specific survival (DSS) rates were 94%, 82%, and 65%, respectively.

DSS was 100% at 20 years of follow-up when negative surgical margins were achieved, compared to 38% at ten years of follow-up (*p*-value < 0.005, Figure 3). Combined transcranial-transfacial approach (CFR) was significantly correlated to better DSS compared to transfacial approach (LR/ESS) only (*p*-value = 0.019, Figure 4). Interestingly, all patients treated with surgery in the last decade (n=7), regardless surgical approach (2 CFR, 2 LR, 2 ESS), had negative surgical margins, and have no evidence of the disease.

A total of seven patients suffered recurrences, of whom five underwent surgery with positive margins. Recurrence free survival (RFS) was 75% at two, and 55% at five and ten years of follow-up. Negative surgical margins and combined transcranial-transfacial approach were correlated to better RFS compared to positive margins and transfacial approach only (78% vs. 29% and 61% vs. 40% at 10 years of follow-up, respectively), but these correlations did not reach statistical significance (*p*-value = 0.107 and 0.184, respectively), probably due to low cohort size. Local recurrence correlated significantly with inferior DSS (*p*-value = 0.022).

Two patients suffered distant metastases (lung and bone) two and 11 years after their primary treatment. Both of these patients have subsequently died from their disease.

Outcomes after non-surgical oncologic treatment

Both patients in this group received chemoradiotherapy, but died of their disease, with neither of them surviving more than 34 months after diagnosis.

Discussion

Sinonasal adenocarcinoma (AC) is a potentially curable disease, despite being an aggressive malignancy with a poor natural history. Sinonasal tumors often have innocuous symptoms, thus leading to delayed diagnosis.[40-42] Late diagnosis explains the high frequency of advanced stage tumors (T3-4); 75% of tumors were T3 and T4 in the present series. The percentages of the different clinical signs in the present study are consistent with published data.[31, 40, 43-46] Nasal obstruction, epistaxis and in many cases visible nasal polyp upon clinical investigation are the main symptoms.

There was a clear correlation between inferior DSS and male sex (p-value = 0.075), intestinal type of tumor differentiation (ITAC; p-value = 0.162), and low grade of tumor differentiation (p-value = 0.078), but these correlations did not reach statistical significance, probably due to low cohort size.

The involvement of key structures such as the anterior skull base (especially the dura mater and the brain), the orbital apex, the cavernous sinus and the infratemporal fossa is recognized in the literature to be a factor influencing survival.[31, 40] These data could not be confirmed in the present study. The absence of statistically significant results could be caused by the effect of generally more aggressive surgical treatment in this cohort resulting in higher rate of radicality, or small size of series.

Nodal involvement at the time of initial diagnosis affects about 10% of reported cases.[47] Distant metastases are rare in this histological type and at this location.[44] There were no patients presenting with nodal involvement, and only 5% of all patients had distant metastasis at the time of diagnosis. Due to the small number of events in this series, it was not possible to highlight the influence of these factors.

Wood dust as a carcinogen was identified in 1995 by the International Agency for Research on Cancer.[48] Other occupational risk factors are leather, tannin, and nickel.[49-51] International literature reports on proportions of patients with wood dust exposure ranging between 12.5% and 96.4%.[31, 40, 43, 44] The GETTEC (Groupe d'etude des Tumeurs de la Tête et du Cou) study found that 84.7% of 418 patients treated for AC were woodworkers, however, it is also described that this proportion is usually higher in European populations (in particular the French population) than in other countries.[52] The mechanism of carcinogenesis is thought to be influenced by the duration and degree of exposure, and the type of wood.[53] The mechanism of carcinogenesis is not completely

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understood, however, several molecular pathways influencing pathogenesis has been identified, e.g. TP53 mutation, CYP1A1 codon 461 polymorphism, GSTM1 null genotype and various epidermal growth factor receptor (EGFR) expression patterns.[54-56] This series report on possible occupational hazard in 45% of all patients – wood dust in 30% - in accordance with the literature. The GETTEC study has also suggested that the prognosis of AC in woodworkers was better than that in non-woodworkers, this correlation could not be observed in our cohort.

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There are no randomized clinical trials to date to guide the treatment of patients with AC and management of the disease is based on observational studies with limited numbers of patients, due to the rarity of the disease. Many studies on AC often include patients with different origins, different stages or histological subtypes pooled from several institutions.[40] Furthermore, AC are so rare that it is unlikely that the impact of multimodal treatment would ever be analysed in a randomized prospective fashion, even within the framework of a multi-institutional study.

There are no trials comparing surgery alone with other treatment regimens. However, in pooled series of varying types of sinonasal malignancies, surgery is more beneficial than other techniques.[57]

Although clear evidence to support the use of XRT in sinonasal adenocarcinoma is difficult to obtain, local control rates of combined treatment strategies for advanced cases are comparable to less advanced cases with surgery alone, suggesting a positive role for postoperative radiotherapy.[40, 58-60] Most data concerning XRT derive from retrospective series and there is understandable selection bias as patients treated with XRT alone are more likely to have locally advanced incompletely resectable tumors and are not comparable to those treated with

surgery alone, as reported in this study as well. Radiotherapy can be avoided in low stage (T1-3) tumors when resection margins are wide, and it should also be avoided for small tumors with limited extension far from the high-risk structures (orbit, cribriform plate, meninges, cavernous sinus, internal carotid artery).[31, 58] In addition, radiotherapy is insufficient when macroscopic excision is incomplete.[61]

The single most important factor influencing long term survival of patients with AC is radical complete surgical resection of the tumor. There is a current debate in AC management about the most appropriate surgical approach. Open (external) surgical procedures have over a long time been considered as the mainstay of treatment, but these approaches are often criticized for higher morbidity. However, critiques often refer to old articles, thereby disregarding the advancements made in this type of surgery over the past two decades. There is a recent trend toward endoscopic resection as primary treatment of AC, as with other sinonasal malignancies, and several authors have reported series of endoscopically resected tumors with comparatively good outcomes.[62-68] There is, however a constant bias in these studies toward the smaller, lower-staged tumors being more suitable for endoscopic resection.

The International Head and Neck Scientific Group evaluated the evidence for treatment strategies in sinonasal adenocarcinoma, concluding with that the ethos to the surgical strategy is to use whichever approach that gains access to remove the whole tumor with a curative intent.[58] Whatever the surgical technique, the bilateral resection of the ethmoid is of paramount importance to minimize the possibility of the appearance of subsequent primary tumors, as in adenocarcinomas, there is histological evidence on the existence of tumor nests in healthy mucosa of areas far from the tumour.[69]

Five-year overall survival rates vary between 21.2% and 78% in the international literature.[40, 42-44, 70, 71] According to published data, adjuvant XRT is used in 38-100% of cases.[31, 40, 42, 43, 45, 70-72] Five-year OS after treatment with surgery was 76% in this series, the next highest rate ever published, after Dulguerov and colleagues.[42] Adjuvant XRT was administered in 89% of all patients. All patients undergoing surgery with negative margins are still NED. The proportion of patients with NED after long-term follow-up is 73% after surgery with combined transcranial-transfacial approach (craniofacial resection), compared to 57%, when only transfacial approach was used. There was only one complication (meningitis) reported after open surgical approach, and there was no perioperative mortality.

Study limitations and strengths

A weakness of this study is that it is based on observational data. Our cohort included patients treated over two decades. Thus, it was subject to the impact of improvements in radiological, surgical, radiotherapy and chemotherapy techniques.

Study strengths were the setting, design and follow-up duration (long term). The data were restricted to one health centre only, reducing the possible confounding effect of differences in access to the healthcare service. Thus, the selection bias that is inherently present in a larger multi-centre study was seemingly avoided. Only end-points that were verifiable were used with respect to the data quality. Lastly, 100% follow-up was obtained.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval

This study was approved by the data protection official at OUH (*ePhorte 2015-5042*). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study does not contain any studies with animals performed by any of the authors.

Informed consent

For this type of study formal consent is not required.

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Legends:

Figure 1: Histological types of primary adenocarcinomas of the sinonasal tract.

Figure 2: Treatment details with final status at the time of last follow-up (percentages are shown as portion of relevant subcohort)

Figure 3: Disease specific survival (DSS) of patients undergoing treatment with curative intent

Figure 4: Disease specific survival (DSS) of patients undergoing treatment with curative intent

Table 1: Demographic, pathologic, and prior treatment information

Table 2: Treatment details

Table 3: Outcomes of the study

Table 1. Demographic, pathologic, and prior treatment information.

Variables	Total
Eligible patients, no. (%)	20 (100)
Age, mean (SD)	58 (16)
Sex, no. (%)	
Male	15 (75)
Female	5 (25)
Occupational hazard, no. (%)	
Wood dusts	6 (30)
Chromium and nickel	2 (10)
Tannins	1 (5)
Presenting symptom, no. (%)	
Nasal stenosis	13 (65)
Epistaxis	2 (10)
Localized pain	2 (10)
Painless swelling	1 (5)
Reduced vision	1 (5)
Distant metastasis	1 (5)
Histology, no. (%)	
ITAC	13 (65)
NITAC, low-grade	4 (20)
NITAC, high-grade	3 (15)
Grade of differentiation, no. (%)	
low	7 (35)
intermediate	8 (40)
high	5 (25)
T stage	
T4	11 (55)
T3	4 (20)
T2	3 (15)
T1	2 (10)
Tumor size (mm), mean (SD)	37 (11)
Affection of adjacent anatomical structures, no.(%)	
Orbita	8 (40)
Meninges	5 (25)
Brain	1 (5)
Bone (microsopic invasion)	10 (50)
Nerve (microscopic invasion)	5 (25)
Vessel (microscopic invasion)	3 (15)

Table 2. Treatment details.

Treatment type	No. of patients (%)
Treatment with curative intent	**18**
Craniofacial resection	
Bifrontal craniotomy + lateral rhinotomy	9 (50)
Bifrontal craniotomy + midfacial degloving	2 (11)
Transfacial resection	
Lateral rhinotomy	4 (22)
Endoscopic sinus surgery	3 (17)
Treatment protocol	
surgery + adjuvant XRT	16 (89)
surgery only	2 (11)
Surgical margins	
Negative	10 (56)
Positive	8 (44)
Non-surgical oncologic treatment	**2**
XRT + ChT	2 (100)
Complications	
Osteonecrosis	1 (5)
Meningitis	1 (5)

Abbreviations: CFR, craniofacial resection. XRT, radiotherapy. ChT, chemotherapy.

Table 3. Outcomes of the study.

Survival function	Cumulative survival (%)			p value
	2-yrs	5-yrs	10-yrs	
Pre-treatment factors				
Age				
≤60 yrs	100	100	100	
>60 yrs	80	47	16	***0.004***
Sex				
Female	100	100	100	
Male	87	62	44	*0.075*
Tumor origin				
ethmoidal sinus	88	81	65	
maxillary sinus	100	0	0	***0.022***
Histology				
non-intestinal-type AC	100	83	83	
intestinal-type AC	85	67	48	*0.162*
Grade of tumor differentiation				
high	100	100	100	
low	87	64	44	*0.078*
Microscopic bone invasion				
no	100	100	83	
yes	80	47	35	***0.041***
Treatment with curative intent				
Overall survival (OS)	**94**	**76**	**61**	
Disease specific survival (DSS)	**94**	**82**	**65**	
Surgical approach				
transcranial+transfacial (CFR)	100	100	79	
transfacial only (LR/EES)	86	46	46	***0.019***
Surgical margins				
Negative	100	100	100	
Positive	88	63	38	***0.005***
Local recurrence				
No	91	91	91	
Yes	86	67	34	***0.022***
Recurrence free survival	**75**	**55**	**55**	
Surgical margins				
Negative	78	78	78	
Positive	71	28	28	*0.107*
Surgical approach				
transcranial+transfacial (CFR)	91	61	61	
transfacial only (LR/EES)	40	40	40	*0.184*
Non-surgical oncologic treatment				
Overall and Disease Specific Survival	**50**	**0**	**0**	

Abbreviations: CFR, craniofacial resection. XRT, radiotherapy. ChT, chemotherapy.