Squamous cell carcinoma of the paranasal sinuses: a single center experience

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

Ethical approval
The study was approved by the data protection official at Oslo University Hospital (OUH; ePhorte 2015-5042). All procedures performed were in accordance with the ethical standards of the institutional and/or national research
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Abstract

**Background:** Squamous cell carcinoma (SCC) of the paranasal sinuses is usually diagnosed at an advanced stage, making curative therapy difficult. The goal of this study was to evaluate the management and outcomes of patients with SCC treated at our institution.

**Methods:** Our prospective database and pathology registry at Oslo University Hospital were searched to identify all patients treated for SCC between 1988 and 2017. Variables extracted from these databases, supplemented by retrospective chart reviews, underwent thorough analysis.

**Results:** 72 patients were included and follow-up was 100%. Mean follow-up was 57 months for the entire cohort, and 108 months for patients with no evidence of disease. 82% of all patients had high-stage (T4) disease at diagnosis. 57 patients underwent treatment with curative intent; consisting of surgery with or without oncologic treatment in 34, and of oncologic treatment only in 23 cases. 17 patients received palliative treatment. The rates of overall survival (OS) for the entire cohort were 55% at two, 41% at five, and 32% at ten years, corresponding disease specific survival rates (DSS) were 55%, 45%, and 34%, respectively. DSS rates after surgical treatment with curative intent were 81% at two, 65% at five, and 54% at ten years. Frequent tobacco use and locally invasive disease were negative prognostic factors. Negative surgical margins were significantly correlated to better survival.

**Conclusions:** Surgical resection with a curative intent yielded a 65% 5-year DSS even in this cohort of patients with high-stage SCC and is still considered as the treatment of choice, preferably in combination with adjuvant radiation- and chemotherapy.

**Keywords:** squamous cell carcinoma; multimodal treatment; survival; outcome; head and neck surgery, neurosurgery
Introduction

Carcinomas originating from the paranasal sinuses are rare, comprising only 3% of all malignancies of the head and neck region (1). Squamous cell carcinoma (SCC) is the most common tumour, arising either de novo or in association with inverted papillomas in approximately 10% of cases (2-8). The paranasal sinuses are anatomically complex, interconnected air-filled spaces which usually allow a tumour to grow to a significant size before symptoms and signs develop. Therefore, most patients present with advanced stage disease and have extensive involvement of adjacent sites at the time of diagnosis (9-15). The tumour sites are usually in close proximity to the orbit, skull base, and the central nervous system, which present particular management difficulties.

Most patients with paranasal sinus SCC undergo surgical resections – if feasible – combined with adjuvant treatment (irradiation and/or chemotherapy). However, the goals of treatment are not limited to curative resection and alternative goals may include oncologic treatment with curative intent, debulking before definitive chemo-radiotherapy, or palliation.

There is a scarcity of prospectively collected data addressing management options and outcomes because of the rarity of this disease (16, 17). Previously identified prognostic factors for SCC include disease stage, site of origin, histopathology, and patient characteristics (16, 17). There is no current evidence suggesting a survival difference between de novo carcinomas and those arising from inverted papillomas (8, 18).

The goal of this study was to evaluate the management of patients with SCC treated at Oslo University Hospital in Norway over the last three decades, and to evaluate our results in light of international literature.
Materials and method

Clinical setting
Oslo University Hospital (OUH) is a tertiary referral centre and the only comprehensive cancer centre in Norway. The catchment area has approximately 3 million inhabitants (56% of the entire Norwegian population), and OUH is responsible for the treatment of all head and neck cancers in this region. In addition, our institution accepts referrals from other health regions in Norway.

Patient cohort
Our prospective database for brain tumours and the pathology registry of head and neck cancers were searched to identify patients eligible for this study. Inclusion criteria were histologically verified SCC and treatment (both surgical and non-surgical) at OUH, from 1988 to date. The medical records of patients were also reviewed retrospectively to record study parameters not included in the database records. Institutional review board ethics approval was obtained.

Tumour-related variables
A histopathological diagnosis of SCC was made by a dedicated head and neck pathologist at presentation. Staging of tumours was based on the TNM staging system of the American Joint Committee on Cancer for maxillary sinus or ethmoid sinus/nasal cavity cancers (19), and evaluated for infiltration of the orbita and skull base (including tumour invasion through the frontal and ethmoid bones towards the anterior skull base, and posteriorly through the posterior bony wall of the maxillary sinus and retromaxillary space towards the middle portion of the skull base). Tumour size was determined from radiographic images at diagnosis. Surgical margins were also retrospectively scrutinized.

Treatment
According to the tumour size and location, the conditions of lymph node and distant metastasis, and the patient’s age, general condition, complications and mental condition, a personalized treatment plan was made for each patient after consultation with the multidisciplinary team (MDT) that included head and neck surgeon, oncologist, pathologist and a radiologist. Neurosurgeons and ophthalmologists were involved in the team when required.

Surgery
The goal of surgery was patient-tailored, depending on tumour stage, patient age and comorbidity. Patients selected for surgical treatment underwent either resection with curative intent (with the goal of achieving negative surgical margins) or palliative surgery (tumour debulking for symptom palliation or radiation volume reduction).
The surgical technique varied based on tumour location and the proximity to vital structures. In general, for resections with curative intent, tumour was resected in an en-bloc fashion, if possible. In cases of a median or paramedian localization with invasion to the nasal cavity, hard palate, and/or maxillary sinus, or primary localization in the medial maxillary sinus or nasal cavity, the lateral rhinotomy or modified midfacial degloving approach was used to provide better visualization. The Weber-Fergusson incision modified by Zange (20) was used in selected cases to perform total hemimaxillectomy in large tumours. The lamina papyracea was resected for tumours extending to the lateral ethmoidal wall. The periorbita was resected in cases of orbital invasion. Tumours infiltrating the orbital fat were treated with orbital exenteration. If an invasion of the anterior skull base was suspected, an additional transcranial approach was done, offering the possibility of a transcranial-transfacial resection of the tumour (i.e. craniofacial resection; CFR). The bony skull base (cribriform plate and fovea ethmoidalis) was resected for tumours involving the bony skull base and dural resections were performed in cases of dura invasion. Brain tissue from the frontal lobe was resected in cases with 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 temporal flap or microvascular flaps. In many cases, an obturator prosthesis was applied 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 initially performed using avascular grafts, but from 1998 onwards, the skull base reconstruction was done using vascularized pericranial flaps. Surgical treatment was deemed adequate if resection margins were negative according to a surgeon and pathologist joint assessment.

Oncologic treatment

From 1988 and to the late 1990s, conventional radiotherapy (XRT) was only given postoperatively as the risk of radiation-induced blindness was significant. In the late 1990s, following the introduction of intensity-modulated RT (IMRT), radiation could be delivered more precise, with conform dose distributions to the tumour, minimizing doses around critical structures, thereby reducing the risk of dry-eye syndrome and preserving vision, without compromising local control (21, 22).
Chemotherapy (ChT) was used up-front for tumour shrinkage when the tumour was deemed inoperable and primary XRT could not be given in adequate doses for tumour control (23, 24). During the last 10-15 years, high-dose XRT (>60Gy) was combined with the oxygen modifier nimorazole and ChT (cisplatinum), as a radiosensitizer during the treatment of SCC, in accordance with the guidelines of the Danish Head and Neck Cancer Group (DAHANCA) (25-30).

**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 (31) and the log rank test was used to test for any significant differences between the survival curves (32). Prognostic factors for OS and DSS were identified using the Cox proportional hazards regression model (33). 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 (34). 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 25 (SPSS Inc., Chicago, USA).
Results

Clinical findings

Ninety patients were identified. Ten patients were excluded due to inadequate data quality. The medical records of 80 patients were subsequently reviewed. Eight patients did not meet the inclusion criteria due to primary treatment elsewhere (7 cases) or insufficient follow-up time (<1 yr; 1 case). Finally, 72 patients were found eligible for this study. The sex distribution showed a clear male predominance with 51 male (71%) and 21 female (29%) patients. All patients were of Caucasian descent. The mean age at diagnosis was 67.1 years (range 36-94 years, 95% CI: 64.0-70.33 years). The peak incidence of disease in our cohort occurred in the seventh decade of life. Frequent tobacco use was present in over to-third (68%) of all patients. Nasal stenosis was the most common presenting symptom - observed in 49% of all cases - followed by local pain (19%), local swelling (31%), and diplopia (1%). Presenting symptoms were predating primary diagnosis by a mean of 4.3 months (range 0.2-27 months, 95% CI: 3.2-5.4). Patient characteristics are summarized in Table 1.

Tumour characteristics

The tumours originated from the maxillary sinus in 60 (83%), from the ethmoid sinus in 8 (11%), and from the frontal sinus in 4 (6%) cases. Invasion of the skull base and orbita was present in 44 (61%) and 42 (58%) cases, respectively. De novo SCC was diagnosed in 60 (83%) cases, while the tumour was arising in association with inverted papilloma in 12 (17%) cases; synchronously in 9 (13%) and metachronously in 3 (4%) cases.

Sixty-six (92%) patients presented with high-stage (T3/T4) tumour. Lymph node status was positive in 14 (19%) cases. Distant metastasis was present at diagnosis in only 3 cases (4%). Tumour characteristics are summarized in Table 1.

Treatment

Treatment with curative intent

Treatment characteristics are summarized in Figure 1 and Table 2. Fifty-seven (79%) of all patients were selected for treatment with curative intent, of whom 34 underwent surgical resections with or without adjuvant oncologic treatment, while 23 patients were deemed inoperable at presentation due to severe comorbidities, and received oncologic treatment only. The vast majority of these patients (82%) had high-stage tumours (T4a in 15, T4b in 7, and T3 in 6 cases, respectively).
The majority of those selected for surgery with curative intent (79%) underwent lateral rhinotomy (LR). In 3 cases, this approach was assisted with endonasal endoscopic surgery. Orbital exenteration was performed in four cases. Six patients underwent craniofacial resection (CFR), while endoscopic resection was the selected surgical method in one case (T2N0M0 tumour).

Negative surgical margins were achieved in 21 (62%) cases, while surgical radicality could not be achieved due to highly invasive tumour growth in 13 (38%) cases. There were no complications relating directly to surgical treatment.

Five (15%) patients underwent surgical treatment only; four of these patients were deemed medically unfit to receive oncologic treatment (advanced age in two, and extensive comorbidity in two cases), while adjuvant XRT was intentionally omitted in one case, due to the proximity of the eye to the irradiation field.

Another five (15%) patients received neoadjuvant XRT, while one patient received neoadjuvant chemoradiotherapy prior to surgical treatment, due to positive lymph node status. All these patients have been treated before 1998.

Primary surgical treatment was combined with adjuvant XRT in 18 (53%) cases, while five patients (15%) received concomitant chemoradiotherapy postoperatively (all treated after 2013).

Twenty-three (32%) patients who underwent oncologic treatment with curative intent received XRT only (12 patients) or XRT with ChT (11 patients), after being considered inoperable upon multidisciplinary evaluation. The vast majority of these patients (19 cases, 83%) presented with locally invasive (stage T4b) disease, while four patients (three with stage 4a and one with stage 3 tumour), could not undergo surgical treatment due to extensive comorbidity. Orbital affection was present in 65%, while affection of the skull base was present in 61% of these patients, respectively. Eight of these patients had positive lymph node status at presentation.

_Treatment with palliative intent_

Fifteen (21%) patients could not receive treatment with curative intent due to locally advanced disease in 13, distant metastases at presentation in one, and advanced age with extensive comorbidity in another case. All patients in this group had orbital affection, while 13 had retromaxillary involvement (including the posterior osseous maxillary wall) in addition. Fourteen patients received palliative XRT, combined with ChT in four cases. Six patients underwent
debulking surgery with LR in four, endoscopic orbitotomy in one, and craniotomy in another case. Treatment characteristics are summarized in Table 2.

Outcomes

We obtained 100% follow-up and the mean follow-up time of the entire cohort was 57 months (range 1–314 months, median 28 months, 95% CI: 40.8–73.2) as of December 31st 2017 (date of final follow-up). The mean follow-up time of patients with no evidence of disease was 108 months (range 66–150 months, median 66 months, 95% CI: 65.8–150.1).

The overall survival rates (OS) for the entire cohort were 55% at two years, 41% at five years, and 32% at ten years of follow-up. Corresponding disease specific survival rates (DSS) were 55%, 45%, and 34%, respectively.

Frequent tobacco use, retromaxillary involvement (including the posterior osseous maxillary wall), metastasis and locally invasive disease at presentation (T4b) were significantly correlated with dismal survival (Table 3). Patients with de novo SCC had worse outcome compared to patients with disease presenting in association with inverted papilloma, but this correlation did not reach statistical significance. We could not find statistically significant correlation between outcome and age, sex, site, or lymph node status.

Outcomes after treatment with curative intent

Half of the patients (50%) who underwent treatment with curative intent were still alive after a mean follow-up time of 61 months (range 4-314 months, median 42 months, 95% CI: 50.1-88.7). Only twelve of these 17 patients died of their disease (DOD), while twenty-one (62%) of all patients in this cohort had no evidence of disease (NED), one (3%) was alive with disease (AWD) at final follow-up.

The OS rates were 81% at two years, 58% at five years, and 49% at 10 years of follow-up. The corresponding DSS rates were 81%, 65%, and 54%, respectively.

The vast majority (86%) of all patients where free surgical margins were obtained had NED at last follow-up. DSS were 90% at two, and 82% at five and ten years of follow-up when negative surgical margins were achieved, compared to 68%, 41%, and 15%, respectively (p=0.002) (Figure 2).
Eight (62%) of all 13 patients with positive surgical margins had local recurrences (after a mean of 19 months), of whom three also developed distant metastases. In contrast, only two (10%) of the 21 patients with negative surgical margins had recurrences (after a mean of 29 months). Survival rates are summarized in Table 3.

Patients undergoing adjuvant XRT and/or ChT had better DSS at five years of follow-up (74% vs. 55% regardless surgical margins, and 51% vs. 25% in case of positive surgical margins), but this difference did not reach statistical significance (p=0.37, p=0.2), probably due to low cohort size.

Combined transfacial-transcranial approach was correlated to better DSS (100% over ten years of follow-up) compared to patients undergoing surgery with only transfacial approach (82% at two, 56% at five, and 0% at ten years of follow-up, respectively) in cases of locally invasive disease at presentation.

Seventeen of all patients selected for oncological treatment with curative intent, but without surgical intervention died of their disease (DOD), while six patients in this group are still alive with their disease (AWD). OS and DSS were 48% after two, 44% after five, and 27% after 10 years of follow-up.

Outcomes after palliative treatment

All 15 patients in this group died of their disease, after a mean survival time of 9.8 months (range, 0.5-33.2 mos, 95% CI 5.1-14.5) OS and DSS were only 7% after two years of follow-up, with no patients surviving longer than 33 months.
Discussion

Squamous cell carcinoma (SCC) is the most frequent malignant tumour of the oral cavity (97%), pharynx and paranasal sinuses (35), but SCC of the paranasal sinuses is quite rare compared to the oral cavity. However, defining the anatomical origin (i.e. gingival vs. paranasal) of the disease may be difficult, as high-stage tumours tend to invade several adjacent structures. The early symptoms of most patients with this disease are not obvious, and by the time patients experience symptoms such as nasal obstruction, localized swelling or pain and then seek initial treatment, the disease often has progressed to an advanced stage (36, 37).

The treatment of SCC is challenging because of the usually advanced T-stage with large tumours and due to anatomic relations and limitations. Treatment methods with curative intent are usually based on all three therapeutic oncological options, namely surgical resection with negative margins, XRT and ChT. Careful patient selection is a cornerstone of successful curative treatment, and multidisciplinary cooperation is inevitable for both patient selection, treatment and adequate follow-up.

According to international literature, the survival rates of patients with SCC are quite dismal. Reported 5-year disease-specific survival rates (DSS) are between 16%-64% (1, 8, 10, 30, 35, 38-54). However, the proportion of patients with advanced disease at presentation in these studies is usually low, leading to obvious selection bias in the survival analysis.

Kermer et al. reported 36 patients with primary resectable SCCs who underwent surgical resection, with or without adjuvant XRT and/or ChT (35). Half of this cohort had T4 stage cancer. However, only 9 (25%) of all patients had tumour originating from the maxilla in the study cohort, while the tumour was affecting primarily the palate and the alveolar ridge (in 16 and 11 cases, respectively).

Bobinskas et al. investigated in 2014 the influence of the site of origin on the outcome of SCC of the maxilla-oral versus sinus (12). They found that maxillary sinus origin was associated with a poorer prognosis on univariate analysis, but this was not confirmed as an independent risk factor by multivariate analysis. Based on their results they concluded, that maxillary sinus origin is not a risk factor for a poorer prognosis itself, rather it is that these tumours are more likely to be advanced at the time of diagnosis and, due to the complex anatomy of the midface, they are more likely to be incompletely resected.
De Almeida et al. reported on 34 patients treated for SCC where 27 underwent definitive surgical resection using endoscopic endonasal approach (EEA) with or without transfacial/transcranial approach. The 5-year disease specific survival rate (DSS) of this cohort including 22 (81%) patients with high-stage disease (T3 and T4) was 62%, with a complication rate of 30% (CSF leak in 18%) (8).

Our study included 72 patients where 92% presented with high-stage disease (T3 and T4). Thirty-four (47%) of these patients were selected for treatment with curative intent including surgery, of whom 82% had high-stage tumour at presentation. All of these patients underwent surgical treatment with or without XRT and/or ChT, and negative surgical margins were obtained in 21 (62%) of cases. The DSS in this cohort was 81% after two, 65% after five and 54% after ten years of follow-up, respectively, and we did not register surgical complications in relation to the treatment.

Only 14% of all patients undergoing radical surgical resection have died of their disease (DOD), while the proportion of patients who DOD was significantly higher after solely oncologic treatment with curative intent (74%), non-radical surgery (69%) or palliative treatment (100%).

Frequent tobacco use, retromaxillary involvement, and metastasis at presentation were identified as individual prognostic factors, correlated significantly to dismal outcome, while negative surgical margins were significantly correlated to better survival.

Best survival in our cohort was achieved with radical surgical resection with or without additional oncologic treatment, leading to significantly higher survival rates than oncologic treatment only with curative intent, or palliative treatment (p=0.004). Oncologic treatment with curative intent in those being deemed inoperable at presentation was associated to significantly better survival than palliative treatment (p=0.001) (Figure 3).

Our study suggests that open surgical resection is still the best treatment option for patients with SCC and our survival rates compare favourably to most series in the international literature. Combined transcranial-transfacial resection was associated with best survival in our cohort, however, the single most important factor impacting long-term survival of these patients is the quality of surgical margins, with radical surgery leading to best survival, regardless of surgical technique.

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

Study strengths were the setting, sample size, 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.
Legends:

**Figure 1:** Treatment details with final status at the time of last follow-up

**Figure 2:** Disease specific survival (DSS) of patients undergoing treatment with curative intent

**Figure 3:** Disease specific survival (DSS) of the entire cohort

**Table 1:** Demographic, pathologic, and prior treatment information

**Table 2:** Treatment details

**Table 3:** Outcomes of the study
References


