# Craniofacial resection of malignant tumors of the anterior skull base – a case series and a systematic review

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**Abbreviations and acronyms**

| | |
|---|---|
| AC | adenocarcinoma |
| ACC | adenoid-cystic carcinoma |
| ASB | anterior skull base |
| AWD | alive with disease |
| BC | Before Christ |
| CFR | craniofacial resection |
| ChT | chemotherapy |
| CI | confidence interval |
| DOD | died of disease |
| DSS | disease specific survival |
| EEA | extended endonasal approach |
| GTR | gross total resections |
| MA | melanoma |
| NED | no evidence of disease |
| ONB | olfactory neuroblastoma |
| OUH | Oslo University Hospital |
| OS | overall survival |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RFS | recurrence free survival |
| RPA | recursive partitioning analysis |
| SA | sarcoma |
| SCC | squamous cell carcinoma |
| SNUC | sinonasal undifferentiated carcinoma |
| XRT | radiotherapy |

**Abstract**

***Background:*** Craniofacial resection (CFR) is still considered as the gold standard for managing sinonasal malignancies of the anterior skull base (ASB), while endoscopic approaches are gaining credibility. The goal of this study was to evaluate outcomes of patients who underwent CFR at our institution and to compare our results to international literature.

***Method:*** Retrospective analysis of all patients undergoing CFR between 1995 and 2017, and systematic literature review according to the PRISMA statement.

***Results:*** 41 patients with sinonasal malignancy (81% with stage T4) of the ASB were included. There was no operative mortality. Complications were observed in 9 cases. We obtained 100% follow-up with mean observation 100 months. Disease-specific survival rates were 90%, 74% and 62% and recurrence-free survival was 85% at two, 72% at five and ten years follow-up, respectively. CFR as primary treatment, *en bloc* resection, and resection with negative margins correlated to better survival. Recursive partition analysis identified the latter as the most important prognostic factor, regardless surgical technique. The relative risk of non-radicality was significantly higher after piecemeal resection compared to *en bloc* resection. Compared to 15 original articles, totaling 2603 patients, eligible for review, the present study has the longest follow-up time, the second highest 5-year OS and the third highest 5-year DSS, despite having a higher proportion of patients with high-stage disease.

***Conclusion:*** CFR in true *en bloc* fashion can still be considered as the treatment of choice in cases of advanced-stage sinonasal malignancies invading the ASB.

**Keywords:** skull base tumors, craniofacial resection, multidisciplinary approach, multimodal treatment, survival

**Introduction**

Anterior skull base procedures – albeit post mortem - were first reported as early as in the 5th century BC by Herodotus, a Greek historian, who described how Egyptian priests removed intracranial contents though the ethmoid sinuses, using a long hook via the nose during the mummification process [13,15]. Dandy described the surgical removal of an orbital tumor with an approach through the anterior cranial fossa, extending his resection through the ethmoids in 1941 [11]. This opened the history of modern craniofacial surgery, but Smith, Klopp and Williams probably documented the first craniofacial resection (CFR) done through separate transcranial and transfacial incisions in 1954 [44]. Their publication was followed by Malecki [32], Ketcham et al. [27,25,26], Clifford [9] and Cheesman et al. [8], who subsequently further developed a combined intracranial and transnasal approach for surgical treatment of anterior skull base tumors.

CFR became technically feasible for an increasing number of patients due to continuous development of surgical and reconstructive techniques [17]. A combined transfacial-transcranial approach proved to be the technique of choice for tumors that breached the anterior cranial fossa because it gave higher rates of gross total resections (GTR) and increased 5-year survival rates of up to 70-80% versus 25% when subtotal tumor resection was followed by adjuvant radiation therapy in certain tumors (e.g., olfactory neuroblastoma and adenocarcinomas) [44,47,29,30]. Over the past decades, continuous improvements of the CFR led to low morbidity rates and excellent cosmesis [17]. Therefore, CFR is still considered the gold standard in the management of malignancies involving the anterior skull base, where the goal of surgery is negative margins with minimal morbidity.

The goal of this study was to evaluate the management of patients who underwent CFR at Oslo University Hospital in Norway from 1995–2017, and to evaluate our results in light of international literature.

## Materials and methods

### *Clinical setting*

Oslo University Hospital (OUH) is a tertiary referral, comprehensive cancer center 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 treatment with CFR at OUH between 1995–2017. 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 was made by a consultant pathologist at presentation. Tumors were assessed for histological grade and stage related to their entity [3,37,18], and evaluated for orbital, dural and/or cerebral infiltration. The tumor site was classified according to the region of presumed origin in tumors affecting several craniofacial bones. Tumor size was determined from the surgical specimens and/or radiographic images at diagnosis, and categorized depending on the maximum length of the tumor in centimeters.

### *Treatment variables*

Patients were discussed by a multidisciplinary team and evaluated regarding the treatment of choice. Decisions were based on patient age and comorbidity, as well as tumor location, size and stage. CFR was defined as a surgical intervention removing the tumor via incisions on the face as well as through the skull, using bifrontal craniotomy in combination with any of the transfacial approaches, including lateral rhinotomy, Weber Ferguson, midfacial degloving and maxillectomy, or endoscopic resection (Figures 1a,1b and 2a, 2b). The surgical procedure was supported by intraoperative neurophysiological monitoring of the III, IV and VI cranial nerves as appropriate, e.g. in cases of orbita involvement. Reconstruction of the dura mater was completed with vascularized galea grafts, supplemented by prophylactic antimicrobial treatment. Surgical treatment was considered adequate if resection margins were negative according to a surgeon and pathologist joint assessment.

All patients underwent multidisciplinary follow-up (neurosurgeon, head and neck surgeon, oncologist and ophthalmologist, if required), for outcome assessments.

***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 craniofacial resection to either death, with or without disease, or last known status. Event-time distributions were approximated using the Kaplan-Meier estimator [20] and the log rank test was used to test for any significant differences between the survival curves [33]. Prognostic factors for OS and DSS were identified using the Cox proportional hazards regression model [10]. 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 [14]. Recursive partitioning analysis (RPA) was used to search for prognostic factors [34]. All possible splits between the variable values seeking to maximize an information measure difference between the two nodes yielding a RPA tree. In our analysis, alpha for stopping the growth of the tree was set at 0.05 and log-rank scores were used for the censored data. 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).

***Search strategy and selection criteria for systematic review***

We conducted a systematic and stepwise literature search according to the PRISMA statement [36] to identify published cases of malignant skull base tumors treated with CFR. Medical subject headings and keywords including, but not limited to, histopathology (e.g., olfactory neuroblastoma, adenocarcinoma, squamous cell carcinoma, etc.), disease location (e.g., sinonasal, skullbase, craniofacial region, etc.), and surgical approach (e.g., craniofacial resection, open resection, etc.) were used to identify studies. All identified studies were screened by title and abstract for further review, and then reviewed for eligibility. Studies were eligible for inclusion if they (I) were published from January 2000 to April 2018, (II) reported on aggregate patient data and/or individual participant data, (III) identified the modality of open craniofacial resection, (IV) reported at least 1 outcome measure related to survival after at least 5 years of follow-up, (V) contained 20 or more patients with different malignant histological entities, and (VI) were primary studies. Publications not available in

English were excluded. When multiple studies were published by a single institution with updated patient follow-up data, or when sub-cohort analysis of already published studies were reported as a separate paper, only the most recent publication, or the publication containing the whole cohort of patients was included to minimize redundancy (Figure 3).

## Results

### *Clinical findings*

The medical records of all 41 patients eligible for inclusion were reviewed. The sex distribution showed a 1:3 male predominance with 29 males (71%) and 12 females (29%). The mean age at diagnosis was 51 years (95% CI: 46.9-55.6 years). The peak incidence of disease in our cohort occurred in the sixth decade of life.

Nasal stenosis was the most common presenting symptom - observed in 78% of all cases - followed by epistaxis (5 cases), painless swelling (two cases), localized pain (one case), and reduced olfaction (one case). Presenting symptoms were predating primary diagnosis by a mean of 9 months (95% CI: 6.1-11.1). Clinical findings are summarized in Table 1.

### *Tumor characteristics*

Cancer types with epithelial origin (carcinomas) were present in 51% of all patients; sinonasal adenocarcinoma (AC) was the histological diagnosis in 11 (27%), sinonasal squamous cell carcinoma (SCC) in 6 (15%), sinonasal undifferentiated carcinoma (SNUC) in 3 (7%), and sinonasal adenoid-cystic carcinoma (ACC) in one (2%) case. Sixteen (39%) patients underwent CFR due to olfactory neuroblastoma (ONB), while sinonasal sarcomas (SA) were present in 4 (10%) patients.

Thirty-three patients (81%) presented with stage T4 disease, while three (7%) had stage T3 and five (12%) stage T2. Two patients had positive lymph node status, while distant metastasis was present in a single case at the time of diagnosis. The mean tumor size was 4.5 cm (95% CI: 3.7-5.2). The tumors affected the orbit in 17 (42%) cases, while dural invasion was observed in 15 (37%) and cerebral invasion in 7 (17%) cases. Tumor characteristics are summarized in Table 1.

### *Treatment*

All patients underwent CFR. A bifrontal craniotomy was the most commonly selected transcranial approach in 36 (88%) cases, while 5 (12%) patients underwent fronto-orbital craniotomy. Bifrontal craniotomy was combined with lateral rhinotomy (LR) in 31 (86%), with midfacial degloving in 4 (11%), and with endoscopic ethmoidectomy in one case (3%). Fronto-orbital craniotomy was combined with LR in all cases.

True *en bloc* resection of the tumor (removal of the specimen in a single piece) could be carried out in 21 (51%) of all cases, whereof 16 (76%) patients had locally invasive (T4) disease. Negative surgical margins were achieved in 18 (86%) of these cases.

A total of 24 (58%) patients underwent radical surgical resection with negative surgical margins, while tumor cells were found in – or close to – the resection margins in 17 (41%) cases; whereof orbital, dural, or cerebral invasions of tumor were present in 11 (65%) (invasion of all three structures in four, of the orbita in four, of the orbita and dura in two, and both dura mater and brain in one case). The tumor resection was true *en bloc* fashion in only three of these patients, while 14 (82%) of all cases of non-radicality occurred after piecemeal resection.

CFR was the primary treatment modality in the majority of cases (90%). Three patients (two patients with SA, one with SNUC) underwent neoadjuvant chemotherapy (ChT), and one patient (with ONB) received neoadjuvant radiotherapy (XRT). In contrast, 33 (83%) patients underwent adjuvant treatment (all with XRT, with additional ChT in one case).

A total of ten (24%) patients suffered local recurrences after a mean latency time of 24 months (95% CI: 13–35.1). Tumor cells were found in, or close to surgical margins after primary surgical treatment in 80% of these cases.

There was no operative mortality. Complications related directly to surgical treatment were observed in 9 cases (22%); epidural hematoma in three, wound infection, epidural abscess and meningitis in two cases each. Cerebrospinal fluid leak did not occur in our cohort. Treatment characteristics are summarized in Table 2.

***Outcomes***

The mean follow-up time of the entire cohort was 100 months (95% CI: 78.2–121.3) and 129 months (95% CI: 100.9–158) for patients with no evidence of disease (NED) as of May 1$^{st}$ 2018 (date of final follow-up). Importantly, none of the patients were lost to follow-up. Twenty-two (54%) patients are still alive, of which 20 have NED, while two patients are alive with disease (AWD). Fifteen patients deceased due to their disease

(DOD), while four patients died of other causes. Only one (4%) patient died of the disease after radical CFR with free resection margins. In contrast, 14 (82%) patients deceased due to their disease after CFR with tumor cells in – or close – to the resection margins on intra- and postoperative investigations.

The OS rates were 88% at two years, 68% at five years and 56% at ten years of follow-up, while corresponding DSS rates were 90%, 74% and 62%, respectively. Actuarial DSS were highest after ten years of follow-up in cases of AC (79%), followed by SA (75%), ONB (60%) and SCC (53%). One patient with SNUC is still NED after 30 months of follow-up (DSS 33%), while no patients survived longer than 30 months with ACC. Overall comparison of survival distribution for the different histological entities in these groups showed significant correlation between histological diagnosis and DSS (p=0.009).

In addition, age under 50 years, invasion of the orbit and tumor size over 5cm, were pre-treatment factors significantly associated with dismal outcome, while we found no significant correlations between survival and sex or affection of the meninges/brain at diagnosis (Table 3).

CFR as primary treatment and *en bloc* resection of the tumor were significantly correlated to better survival. In addition, DSS of patients undergoing treatment with adequate CFR (with negative surgical margins) was 100% after two years, and 95% after 20 years of follow-up (only one patient had DOD in this group). Positive surgical margins were significantly correlated to dismal outcome compared to negative margins (DSS 20% vs. 95% after 10 years of follow-up).

Negative surgical margins were identified by recursive partition analysis (RPA) as the single most important prognostic factor, while we could not find significant correlations between survival and surgical technique or the type of adjuvant therapy.

Recurrence-free survival (RFS) of the entire cohort was 85% at two years, and 72% at five and ten years follow-up. CFR with negative surgical margins was significantly correlated with better RFS (91% vs. 33% after 10 years follow-up). CFR with true *en bloc* resection was also correlated to superior RFS than piecemeal resection (85% vs. 51% after 5 and 10 years of follow-up), however, there were only three patients who suffered recurrences in the former group compared to 8 in the latter, leading to non-significant correlation between resection type and RFS. Outcome details are summarized in Table 3.

**Systematic literature review**

The literature search identified at total of 1017 studies, of which 838 were excluded (studied other diseases, non-original studies, studied non-surgical treatments, duplicate studies). Of the remaining 179 articles, 89 were published before year 2000, 2 did not identify open craniofacial resection as the surgical treatment, 11 had no sufficient survival data, 14 studied fewer than 20 patients with various malignant histologies, while 4 articles were reporting on sub-cohorts of previously published studies. After applying the aforementioned criteria, 14 retrospective case series [6,4,5,19,17,48,28,12,2,7,1,35,39,43] and one international collaborative study [40] were eligible for further review, totaling 2603 patients (1296 and 1307, respectively) (Figure 1).

Twelve series provided sufficient information regarding treatment plan (Table 4). CFR was the first surgical procedure after diagnosis in an average of 72% of all cases (range 51-96%, median 72%, 95% CI 62.5-80.8). Four studies included patients with benign histology also (totaling 66 cases). All study cohorts included patients with SCC and AC. ONB and SA were not present in two, ACC in four, while MA and SNUC were absent in six series. The most common histology was SCC (26%), followed by AC (21%), ONB (13%), SA (10%), melanomas (MA, 4%), adenoid-cystic carcinomas (ACC) and SNUC (3% each), while 19% of all cases represented rare malignant histological entities. Only seven studies reported on TNM staging, the proportion of cases with T4 stage in these studies averaged 68% (ranging from 29% to 100%).

Average follow-up time was reported in twelve studies (Table 4), with the mean length of 53 months (95% CI: 39.4–66.4). OS after five years of follow-up was reported in 13 series (which of one included benign cases also during survival analysis), ranging from 46% to 72% (median 54%). DSS after five years of follow-up was reported in 9 publications ranging from 46% to 78% (median 60%), while RFS was analyzed in only 7 studies ranging for 38% to 71% (median 42%). Data regarding complications related to surgery was available in 13 studies with a mean of 31% (95% CI 24-37.6), while information regarding peroperative mortality was present in 12 series (0% in two series) averaging 4% (95% CI 1.6-7.3%).

**Discussion**

Since its introduction more than 50 years ago, craniofacial resection (CFR) has undergone several important technical improvements, and the subsequent addition of plastic and reconstructive surgeons and radiation and medical oncologists to the team provided a comprehensive approach to the management of lesions previously thought to be inoperable or associated with significant surgical morbidity.

The varied pathology of lesions involving the skull base makes it difficult to accrue large series of patients with uniform pathologies. With only a few multi-institutional studies published to date, most reports in the literature are single center series with a limited number of patients and often short follow-up times, making results difficult to interpret and compare.

The goal of this study was to evaluate the management of all 41 patients who underwent CFR as part of their primary treatment at our institution over the last two decades.

The distribution of histological diagnoses in our study is in accordance with the available literature, identifying SCC, AC and ONB as the three most common pathologies treated by open CFR, followed by SA, MA, ACC and SNUC, representing a significantly smaller proportion of cases [6,4,40,5,19,17,48,28,12,2,1,35,7,39,43].

We obtained 100% follow-up over the longest time period reported in the available literature, being almost twice as long as the average in the reviewed series (100 mos vs. 53 mos). We also report the highest RFS after 5 years of follow-up. Only one study [35] reported a higher 5 year OS and only two series [35,48] had better 5 year DSS; TNM stage was described in only one of these series [35], showing much lower proportion of T4 cases compared to our cohort (66% vs. 81%). The follow-up times in these series were also significantly shorter (42 and 70 mos in average). We identified two series reporting lower complication rates compared to our results [6,28], but none of these provide information regarding TNM stage.

The negative prognostic factors for survival identified in our study are in accordance with the international literature; positive surgical margins, tumor size, orbital invasion, and histological diagnosis of SNUC/ACC. Cerebral invasion of the tumor at presentation was also correlated to dismal outcome, but this correlation did not reach statistical significance (p=0.245). We have also found that patients younger than 50 years at the time of diagnosis have worse outcome, this paradox correlation could be explained by more aggressive histological entities affecting younger patients.

Our results after CFR for malignant tumors of the anterior skull base regarding survival, complication rate and mortality, compare well to meta-analyses of endoscopic techniques [41,16]. However, our cohort includes a higher proportion of patients with tumors of high stage, and the results are analyzed after a much longer follow-up time (Table 4).

Recursive partition analysis (RPA) identified negative surgical margins as the most important prognostic factor regarding survival, regardless surgical technique. In our hands, negative surgical margins were obtained significantly more frequently when a true *en bloc* resection was performed as opposed to a fragmented resection. While negative margins were achieved in 86% of all cases where resection was completed in a true *en bloc* fashion, only 30% of all patients could benefit from the same advantage regarding survival after undergoing piecemeal resections (relative risk 4.9, $p < 0.001$), highlighting the significant role of the former technique.

The endonasal endoscopic skull base approach - developed from concepts applied from the field of rhinology and functional endoscopic sinus surgery – was introduced in the 1980s, revolutionizing the treatment of inflammatory diseases and lesions limited to the sinonasal tract [45]. Regarding tumors, this approach was initially limited to benign pathologies not extending up to the anterior skull base [31]. The first reports on pure endoscopic techniques alone or in combination with frontal craniotomy (cranio-nasal approach, endoscopic assisted craniotomy) emerged in the late 1990s [31,46,49,42]. Following the publication of several series analyzing small and intermediate-size cohorts of patients, there has been considerable criticism from physicians believing that endoscopic surgery by its very nature does not adhere to the principles of oncologic surgery – that is, the tumor is removed in a piecemeal fashion, and a true *en bloc* resection is not achieved [38,31].

Our data demonstrates that we managed to obtain a significantly higher proportion gross total resection with microscopic negative margins when performing resection in a true *en bloc* fashion as opposed to piecemeal resection. Despite the development of newer endoscopic techniques, like the extended endonasal approach

(EEA) [22,21,23,24] providing the possibility of fragmented resection of tumors, traditional, open CFR (and hence resection in true *en bloc* fashion) continue to play and important role in skull base surgery and is considered as gold standard and primary strategy in the treatment of advanced anterior and anterolateral skull base malignancies.

In our opinion, open CFR with radical *en bloc* resection can still be considered as the treatment of choice in cases of aggressive and invasive anterior skull base and sinonasal malignancies, alongside with endoscopic techniques, mainly targeting for lower stage and more limited tumors.

**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 during this time period. We have also excluded patients with malignant melanoma, making our cohort less complete.

Study strengths were the setting, sample size, design and follow-up duration (long term). The data were restricted to one health center 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-center study was seemingly avoided. Only end-points that were verifiable were used with respect to the data quality. Lastly, 100% follow-up was obtained.

**Funding**

No funding was received for this research.

**Conflict of interest**

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

**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.

**Legends**

**Fig. 1 Preoperative MRI of a patient with olfactory neuroblastoma stage T4bN0M0 (1a: coronal plane, 1b: sagittal plane)**

**Fig. 2 Postoperative MRI after craniofacial resection of a patient with olfactory neuroblastoma stage T4bN0M0 (2a: coronal plane, 2b: sagittal plane)**

**Fig. 3** The PRISMA study flow diagram for our systematic and stepwise literature search

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

**Table 2** Treatment details

**Table 3** Outcomes of the study

**Table 4** Summary of studies included in systematic review

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