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ORIGINAL ARTICLE - NEUROSURGICAL TECHNIQUE EVALUATION

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

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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 Forty-one 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 of 100 months. Disease-specific survival rates were 90%, 74%, and 62% and recurrence-free survival was 85% at two, 72% at five, and 10 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 of 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

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

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SCC Squamous cell carcinoma
SNUC Sinonasal undifferentiated carcinoma
XRT Radiotherapy

Introduction

Anterior skull base procedures—albeit postmortem—were first reported as early as in the fifth century BC by Herodotus, a Greek historian, who described how Egyptian priests removed intracranial contents through 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. [25–27], 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) [29, 30, 44, 47]. 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 to 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 and 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, 18, 37], 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 (Fig. 1a, b) and (Fig. 2a, b). 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

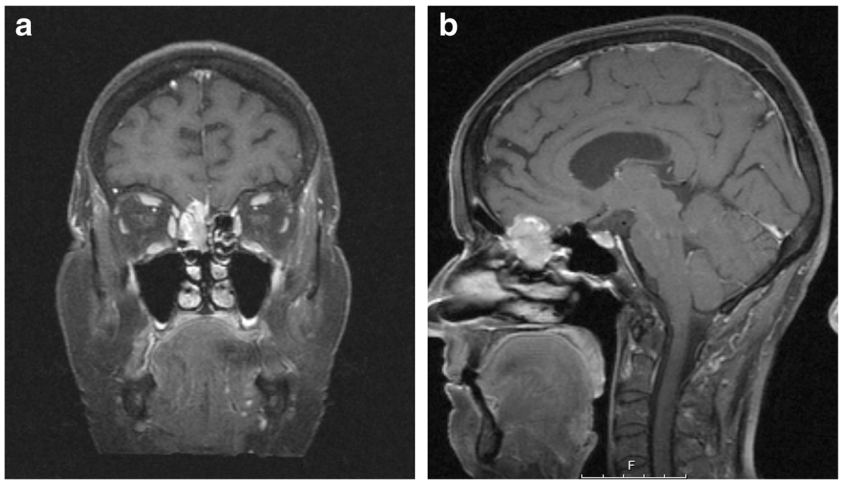

Fig. 1 Preoperative MRI of a patient with olfactory neuroblastoma stage T4bN0M0 (**a** coronal plane, **b** sagittal plane)

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, skull base, 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

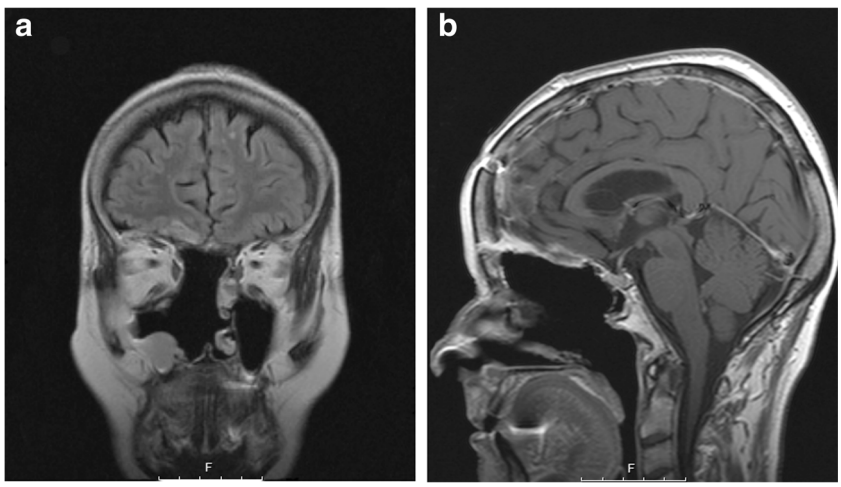

Fig. 2 Postoperative MRI after craniofacial resection of a patient with olfactory neuroblastoma stage T4bN0M0 (**a** coronal plane, **b** sagittal plane)

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 subcohort 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 (Fig. 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).

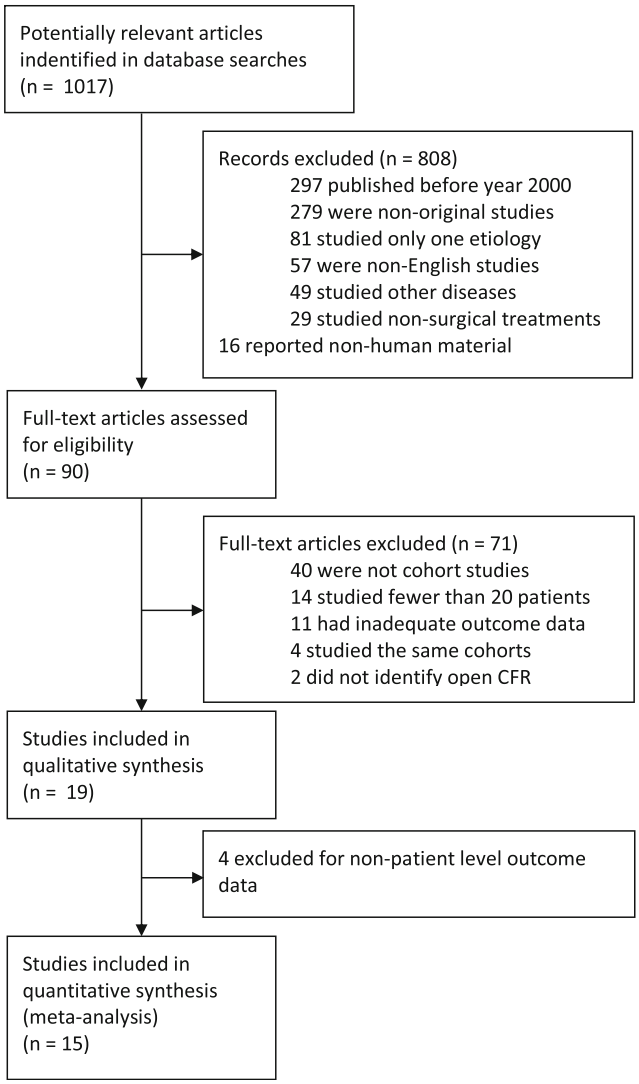

Fig. 3 The PRISMA study flow diagram for our systematic and stepwise literature search

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

Table 1 Demographics, pathologic, and prior treatment information

Variables	Total
Eligible patients, no. (%)	41 (100)
Age, mean (SD)	51 (14)
Sex, no. (%)	
Male	29 (71)
Female	12 (29)
Presenting symptom, no. (%)	
Nasal stenosis	32 (78)
Epistaxis	5 (12)
Painless swelling	2 (5)
Localized pain	1 (2)
Reduced olfaction	1 (2)
Histology, no. (%)	
Carcinoma	20 (51)
Adenocarcinoma	11 (27)
Squamous cell carcinoma	6 (15)
Sinonasal undifferentiated carcinoma	3 (7)
Adenoid cystic carcinoma	1 (2)
Olfactory neuroblastoma	16 (49)
Sarcoma	4 (10)
T stage	
T4	33 (81)
T3	3 (7)
T2	5 (12)
Tumor size (mm), mean (SD)	44.8 (21)
Affection of adjacent anatomical structures, no. (%)	
Orbita	17 (42)
Meninges	15 (37)
Brain	7 (17)

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%) had 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.

Table 2 Treatment details

Treatment type	No. of patients (%)
Craniofacial resection	41 (100)
Transcranial approach	
Bifrontal craniotomy	36 (88)
Fronto-orbital craniotomy	5 (12)
Transfacial approach	
Lateral rhinotomy	36 (88)
Midfacial degloving	4 (10)
Endoscopic ethmoidectomy	1 (2)
Resection type	
True en bloc	21 (51)
Piecemeal	20 (49)
Surgical margins	
Negative	24 (59)
Positive	17 (41)
Treatment option	
CFR + XRT	31 (76)
CFR only	5 (13)
ChT + CFR	2 (5)
XRT + CFR	1 (3)
CFR + XRT + ChT	1 (3)
ChT + CFR + XRT	1 (3)
Complications	
Total	9 (22)
Epidural hematoma	3 (8)
Wound infection	2 (5)
Epidural abscess	2 (5)
Meningitis	2 (5)
Cerebrospinal fluid leak	0 (0)

CFR, craniofacial resection; *XRT*, radiotherapy; *ChT*, chemotherapy

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, 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 2 years, 68% at 5 years, and 56% at 10 years of follow-up, while corresponding DSS rates were 90%, 74%, and 62%, respectively. Actuarial DSS were highest

after 10 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 5 cm, were pretreatment 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).

Table 3 Outcomes of the study

Survival function	Cumulative survival (%)			*p* value
	2 years	5 years	10 years	
Overall survival (OS)	88	68	56	
Disease-specific survival (DSS)	90	74	62	
Pretreatment factors				
Age				
> 50	100	95	68	
≤ 50	78	50	50	0.032
Invasion of the orbita				
No	96	87	77	
Yes	81	55	37	0.024
Tumor size (mm)				
≤ 50	95	91	78	
> 50	67	44	44	0.032
Histology				
AC	100	100	79	
SA	75	75	75	
ONB	88	69	60	
SCC	80	80	53	
SNUC	67	33	n/a	
ACC	100	0	0	0.009
Treatment factors				
Primary treatment				
CFR	94	80	66	
XRT/ChT	50	25	25	0.022
Surgical margins				
Negative	100	95	95	
Positive	77	47	20	< 0.001
Resection type				
True en bloc	100	85	78	
Piecemeal	80	64	45	0.016
Recurrence-free survival	85	72	72	
Surgical margins				
Negative	91	91	91	
Positive	76	33	33	0.001

CFR, craniofacial resection; *XRT*, radiotherapy; *ChT*, chemotherapy

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 2 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 2 years, and 72% at 5 and 10 years of follow-up. CFR with negative surgical margins was significantly correlated with better RFS (91% vs. 33% after 10 years of 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 subcohorts of previously published studies. After applying the aforementioned criteria, 14 retrospective case series [1, 2, 4–7, 12, 17, 19, 28, 35, 39, 43, 48] and one international collaborative study [40] were eligible for further review, totaling 2603 patients (1296 and 1307, respectively) (Fig. 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

Table 4 Summary of studies included in systematic review

Author	Year	Period	Institution	*n* (CFR)	F/O time (mos)	OS 5 year	DSS 5 year	RFS 5 year	Complication rate	Mortality	T4 proportion	Histology
Bridger et al.	2000	1975–1996	Prince of Wales Hospital, Australia	73	84	61%	69%	59%	12%	0%	n/a	AC (27), SCC (20), ONB (14), MA (4), ACC (3), SA (2), other (3)
Bentz et al.	2003	1973–2000	Memorial Sloan-Kettering Cancer Center, USA	166	53	52%	57%	41%	43%	5%	n/a	SCC (40), SA (32), AC (20), ONB (20), MA (17), SNUC (8), other (29)
Patel et al.	2003	1956–2000	International Collaborative Study, 17 institutions	1307	25	54%	60%	53%	33%	4%	47%	SCC (375), AC (210), ONB (151), SA (146), MA (53), other (372)
Bilsky et al.	2005	1996–2002	Memorial Sloan-Kettering Cancer Center, USA	25	n/a	56%	n/a	41%	24%	4%	n/a	SA (9), SCC (6), ACC (3), AC (2), other (5)
lanetti et al.	2005	1986–2003	La Sapienza, Rome, Italy	24	75	51%	n/a	n/a	n/a	n/a	75%	AC (7), SCC (6), ACC (4), SNUC (3), SA (2), ONB (1), other (1)
Howard et al.	2006	1978–2004	University College London, UK	308	63	65%	59%	n/a	32%	2%	n/a	AC (62), ONB (56), SA (43), SCC (34), ACC (19), SNUC (15), MA (8), other (22), benign (49)
Wong et al.	2006	1993–2003	Queen Mary Hospital, Hong Kong	39	42	n/a	78%	n/a	26%	0%	n/a	ONB (13), SNUC (5), SA (5), SCC (3), AC (2), ACC (1), other (5), benign (5)
Kim et al.	2008	1989–2006	Seoul National University Hospital, Korea	46	25	47%	n/a	n/a	20%	n/a	n/a	ONB (19), SCC (7), SA (5), MA (3), AC (1), SNUC (1), other (4), benign (6)
Eloy et al.	2009	1997–2006	University of Miami/Jackson Memorial Medical Center, USA	48	25	n/a	n/a	n/a	25%	17%	29%	SCC (25), ACC (8), ONB (4), AC (4), SNUC (2), MA (2), SA (2), other (1)
Albu et al.	2011	1996–2008	University of Medicine and Pharmacy Cluj-Napoca; Romania	64	12–90	47%	n/a	n/a	n/a	n/a	n/a	SCC (20), AC (14), ACC (8), SA (8), ONB (7), MA (4), other (3)
Abuzayed et al.	2011	1999–2009	Cerrehpasa Medical Faculty, Istambul, Turkey	27	74	62%	n/a	n/a	30%	7%	n/a	SCC (5), SA (4), AC (3), ACC (2), ONB (1), other (6), benign (6)
Mine et al.	2011	1992–2009	Chiba University, Japan	32	70	72%	75%	71%	47%	3%	66%	SCC (12), SA (6), ONB (4), AC (3), ACC (2), MA (2), other (3)
Cantu et al.	2012	1987–2007	Istituto Nazionale dei Tumori, Milano, Italy	366	n/a	46%	46%	38%	30%	4%	58%	AC (178), SCC (44), ONB (36), SNUC (34), ACC (24), MA (15), other (35)
Nishio et al.	2015	1992–2011	Nagoya University Hospital, Japan	40	40	53%	63%	n/a	53%	2%	100%	SCC (32), ACC (2), AC (2), SNUC (1), other (3)
Sakata et al.	2016	1984–2012	Kurume University Hospital, Japan	38	59	56%	59%	42%	26%	5%	100%	SCC (25), ONB (6), AC (2), SA (2), ACC (1), SNUC (1), other (2)
König et al.	2018	1995–2017	Oslo University Hospital, Norway	41	100	68%	74%	72%	22%	0%	81%	ONB (16), AC (11), SCC (6), SA (4), SNUC (3), ACC (1)

AC, adenocarcinoma; *SCC*, squamous cell carcinoma; *ONB*, olfactory neuroblastoma; *MA*, melanoma; *ACC*, adenoid cystic carcinoma; *SA*, sarcoma; *SNUC*, sinonasal undifferentiated carcinoma

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 5 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 5 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 preoperative 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 [1, 2, 4–7, 12, 17, 19, 28, 35, 39, 40, 43, 48].

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 [16, 42]. 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 of 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, 41, 46, 49]. 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 [31, 38].

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) [21–24], 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.

Compliance with ethical standards

Conflict of interest The authors declare that they have 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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