Delayed Complications after Anterior Craniofacial Resection of Malignant Skull Base Tumors

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Abstract

Objective To report complications occurring at least 6 months after completion of treatment for patients with anterior skull base malignancy undergoing anterior craniofacial resection (CFR).

Design Retrospective review of medical records of all patients undergoing traditional CFR for treatment of anterior skull base malignancy from 2002 through 2011.

Setting Massachusetts General Hospital/Massachusetts Eye and Ear Infirmary Cranial Base Center.

Participants Thirty-one consecutive patients who had at least 18 months of follow-up for analysis were reviewed. All patients underwent traditional CFR. A total of 28 patients received postoperative proton beam radiation therapy. Eleven patients received adjuvant chemotherapy.

Main Outcome Measures A delayed complication was any complication occurring at least 6 months after the completion of treatment.

Results Seventeen patients had delayed complications. Orbital complications were the most common type (13 patients) followed by issues with wound healing (6 patients). The most common orbital complication was epiphora (7 patients). The most common wound complication was a nasocutaneous fistula (5 patients).

Conclusions Patients with anterior skull malignancy can develop complications months to years after the completion of treatment. Therefore, it is important to continue to follow and report complications for several years when deciding on the optimal approach for treatment of these patients.

Keywords
- complications
- anterior craniofacial resection
- skull base
- anterior skull base malignancy

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Introduction

The traditional anterior craniofacial resection (CFR) has been the main surgical approach for the treatment of malignant anterior skull base tumors since Ketcham's first description of the procedure in 1963.[1–3] Over the last several decades, surgical techniques have advanced and perioperative management has improved for patients with these tumors, which has resulted in a decreased rate of complications.[4] The development of endoscopic approaches to the skull base, innovative options for reconstruction, and the use of broad-spectrum antibiotics have contributed to these improvements. Operative mortality rates are reported to be $< 5\%$, but the overall complication rate for traditional CFR has still been reported to range from 25% to 65%.[3–12]

Previous studies have discussed early and late complications of CFR. The definition of an early complication is not consistent in all studies but has been labeled as up to 30 days after surgery.[4] In a study by Dias et al, late complications (defined as occurring $>$ 14 days after surgery) were reported and included any complications noted up to 5 months after treatment.[10] The goal of these studies was to report complications related to the surgery itself. However, most patients with anterior skull base malignancy are not treated with surgery alone. Very few publications in the literature describe complications occurring many months or years after completed therapy. In our experience, complications from combined modality treatment for anterior skull base malignancy can appear in a delayed fashion and therefore are often not reported. The purpose of this study is to review delayed complications, which we define as $>$ 6 months posttreatment, in patients with malignant tumors of the anterior skull base treated with traditional anterior craniofacial surgery and adjuvant therapy. Immediate and early complications were also recorded and reviewed in this study.

Patients and Methods

A retrospective review was conducted of all patients undergoing traditional CFR for treatment of malignant anterior skull base disease at the multidisciplinary Massachusetts General Hospital/Massachusetts Eye and Ear Infirmary Cranial Base Center from 2002 to 2011. Our study cohort included 48 patients, 30 men and 18 women. There was one mortality in the postoperative period. Patients with $<$ 18 months of follow-up, gross residual disease after resection, and who underwent revision CFR were excluded from our study. In addition, patients with residual disease after resection were excluded from analysis because of the potential confounding factor that persistent disease could be the cause of the complication. This resulted in 31 patients for the analysis of complications. Of these patients, the mean age at diagnosis was 51 years with an age range of 12 to 82 years. All patients had malignant tumors of varying histologies (►**Table 1**). Of the 31 patients included in the analysis, 28 patients received postoperative proton beam radiation therapy. The median dose of radiation was 63.7 Gy (range: 16.2–72 Gy). Eleven patients also received adjuvant cisplatin-based chemotherapy. Consideration of postoperative chemoradiation was given to patients with positive microscopic margins, dural involvement, and advanced stage disease.[13]

Table 1 Tumor histology

Pathology	No. of patients
Squamous cell carcinoma	3
Olfactory neuroblastoma	17
Melanoma	2
Sarcoma	2
Adenoid cystic carcinoma	1
Sinonasal undifferentiated carcinoma	3
Adenocarcinoma	2
Basal cell carcinoma	1

All patients underwent traditional anterior CFR via a lateral rhinotomy and bifrontal craniotomy. During the course of the lateral rhinotomy incision and exposure of the sinonasal cavity, the lacrimal sac was identified, transected, and marsupialized. A standard frontal osteotomy was performed above the root of the nasal bone. If the tumor involved the nasal bone, it was resected en bloc. The frontal sinus was cranialized in all cases. Two patients required concurrent orbital exenteration at the time of CFR. The combined orbital and skull base defect was reconstructed with a rectus abdominis free flap in one patient and a radial forearm free flap in the other patient. One additional patient underwent a total rhinectomy at the time of CFR and was reconstructed with a radial forearm free flap. All other patients were reconstructed with a pericranial flap. Lumbar drainage was not used for any of the patients in this study. Antibiotic prophylaxis was administered before the start of the procedure. The typical regimen included vancomycin, a third-generation cephalosporin, and metronidazole. This regimen was altered if there was an antibiotic allergy concern. Antistaphylococcal antibiotics (typically cephalexin) were continued until the nasal packing was removed (typically removed on postoperative day 7). If there was a concern for a postoperative infection, the infectious disease service was consulted and antibiotics were tailored to address culture results.

We defined an early complication as any complication occurring within 6 months of completion of treatment. A delayed complication was defined as any complication occurring at least 6 months after the end of treatment. Complications were characterized into four categories: intracranial (cerebrospinal fluid [CSF] leak, encephalocele, meningitis, encephalitis, stroke, intracranial bleed), wound (cellulitis, incisional infection or dehiscence, bone flap infection, nasocutaneous fistula), orbital (epiphora, diplopia, optic neuropathy, retinopathy, keratopathy), and mortality (►**Tables 2** and **3**).

To identify patient and tumor factors predictive of complications, the variables of age, gender, orbital involvement, intracranial involvement, adjuvant radiation therapy, and adjuvant chemotherapy were analyzed by univariate analysis

Table 2 Early complications

	Age at diagnosis, y	Diagnosis	Orbital involvement	Brain involvement	RT	Chemotherapy	Orbital complications	Intracranial complications	Wound complications
1	67	ONB	No	Yes	Yes	Yes		Intracranial infection	
2	62	ONB	No	No	Yes	No			Periorbital cellulitis
3	44	ONB	No	No	Yes	No	Diplopia		
4	51	ONB	No	No	Yes	No		Intracranial infection	
5	21	ONB	No	No	Yes	Yes	Diplopia		
6	42	SNUC	No	No	Yes	Yes			Facial cellulitis
7	56	Fibrosarcoma	No	No	Yes	No		Intracranial infection	
8	64	SNUC	No	Yes	Yes	Yes			Facial cellulitis
9	45	SCCa	Yes	No	Yes	Yes			Nasocutaneous fistula
10	63	AdenoCa	No	No	No	No			Nasocutaneous fistula
11	29	ONB	No	No	Yes	Yes			Periorbital cellulitis

Abbreviations: AdenoCa, adenocarcinoma; ONB, olfactory neuroblastoma; RT, radiation therapy; SCCa, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.

Table 3 Late complications

Patient	Age at diagnosis, y	Diagnosis	Orbital involvement	Brain involvement	RT	Chemotherapy	Orbital complications	Intracranial complications	Wound complications
1	67	ONB	No	Yes	Yes	Yes	Ectropion Radiation Keratopathy		Nasocutaneous fistula
2	62	ONB	No	No	Yes	No	Diplopia		
3	44	ONB	No	No	Yes	No	Vitreous hemorrhage		
4	51	ONB	No	No	Yes	No	Epiphora Diplopia on extreme gaze	Encephalocele CSF leak Cerebritis	
5	21	ONB	No	No	Yes	Yes	Retinal hemorrhage		
6	42	SNUC	No	No	Yes	Yes	Radiation retinopathy		Peri-orbital cellulitis
7	56	Fibrosarcoma	No	No	Yes	No	Epiphora		
8	64	SNUC	No	Yes	Yes	Yes	Radiation retinopathy		
9	45	SCCa	Yes	No	Yes	Yes		Encephalocele	Nasocutaneous fistula ORN
10	75	SCCa	Yes	No	Yes	No	Epiphora		
11	19	SNUC	No	Yes	Yes	Yes			Nasocutaneous fistula
12	63	ACC	No	No	Yes	No			Nasocutaneous fistula
13	77	ONB	No	Yes	Yes	No	Epiphora		
14	11	ONB	No	No	Yes	No	Epiphora		
15	63	ONB	No	No	Yes	No	Epiphora Diplopia	Frontal lobe radiation injury	Periorbital cellulitis Nasocutaneous fistula
16	82	BCC	No	No	Yes	Yes	Epiphora		
17	21	ONB	No	Yes	No	No		Intracranial infection	

Abbreviations: ACC, adenoid cystic carcinoma; ONB, olfactory neuroblastoma; ORN, osteoradionecrosis; RT, radiation therapy; SCCa, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.

by chi-square tests. Statistical analysis was performed using JMP v.10 software (SAS, Cary, NC). A p value < 0.05 was considered statistically significant.

Results

In our series of 48 patients undergoing open anterior CFR for skull base tumors, there was one perioperative mortality (2.3%). Of these 48 patients, 31 patients were resected without gross disease remaining and had at least 18 months of follow-up. Eleven patients developed early complications (35.5%); 17 patients developed delayed complications (54.8%). In the 11 patients with early complications, there were 6 wound complications, 3 intracranial (central nervous system) complications, and 2 orbital complications (some patients had more than one type of complication). Of the 17 patients with delayed complications, there were 13 patients with orbital complications, 6 patients with wound complications, and 4 patients with intracranial complication (some patients had more than one type of complication). ►**Tables 2** and **3** provides further details.

Seventeen patients had delayed complications from their therapy. Of these patients, six patients had delayed wound complications with a mean time from treatment of 14 months. One patient developed delayed facial cellulitis related to a concomitant maxillary sinusitis that required intravenous antibiotic therapy and eventual endoscopic sinus surgery to improve drainage of the maxillary sinus. Five patients developed a nasocutaneous fistula in the medial canthal region, and two of these patients required free flap reconstruction. The other three patients with small nasocutaneous fistulas declined surgical treatment. Fig. 1 shows a radiographic example of one of the patients with nasocutaneous fistula. All of the patients who developed nasocutaneous fistula required partial nasal bone resection at the time of initial surgery due to the extent of tumor involvement, and it was believed the wound breakdown was likely related to the compromised nasal bone support. Of the 17 patients with delayed complications, 4 patients developed intracranial complications. One patient developed breakdown of the pericranial flap reconstruction that led to an encephalocele and CSF leak 19 months after treatment. This patient underwent a transcranial repair with a free fascia lata graft with complete resolution of the spinal fluid leak. The other patient with encephalocele also had a medial canthal defect, and both were repaired with an anterior lateral thigh flap, with resolution of both the encephalocele and the medical canthal defect. Thirteen patients developed delayed orbital complications. Seven patients developed epiphora, three patients developed diplopia, two patients developed radiation retinopathy, one patient developed ectropion, two patients developed intraorbital hemorrhage, and one patient developed radiation keratopathy leading to blindness (some patients developed more than one type of orbital complication). No cases of frontal sinus mucocele were encountered in the series. ►**Table 3** lists further details.

A total of 9 of the 11 patients (82%) who had early complications went on to develop delayed complications after the completion of therapy. Patients who developed early and late complications are listed as the same first nine patients in ►**Tables 2** and **3**. One of these patients (Patient 9) developed a medial canthal defect early after surgery. The defect was closed, but despite a successful initial closure, a persistent nasocutaneous defect developed after completion of therapy. This was eventually repaired with free flap reconstruction.

►**Table 4** investigates which variables were potentially predictive of early and delayed complications including age, gender, orbital invasion, intracranial invasion, chemotherapy, and radiation therapy. We also performed separate univariate analysis looking at whether these variables were predictive of delayed orbital, wound, or brain complications separately. Adjuvant radiation therapy showed a trend toward predicting delayed orbital complications ($p < 0.06$). Using univariate analysis, none of the variables studied were found to be statistically significant in predicting either early or delayed complications; therefore multivariate analysis was not performed.

Discussion

Since the technique of anterior craniofacial surgery was first described by Ketcham et al in 1963, it has become the standard method of open surgical treatment of malignancies of the anterior skull base.[1–3] Although advances in surgical resection and reconstruction have reduced overall complication rates, both immediate and delayed complications continue to occur in the setting of CFR and adjuvant chemoradiation therapy.

Several studies in the literature have reported postoperative complication rates after open anterior CFR ranging from 25% to 65%.[3–12] In 1994, Kraus et al reviewed 85 consecutive patients undergoing anterior CFR with local major complications occurring in 26 patients (31%), local minor complications in 7 patients (8%), and systemic complications in 5 (6%).[9] They identified advanced age, dural resection, and the use of a pedicled pericranial flap as risk factors for the development of local major complications (age and dural resection showed a trend but did not reach statistical significance).

Similarly, Deschler et al reviewed 52 patients undergoing CFR. They reported a complication rate of 40% with infection the most common. Neither prior chemotherapy nor radiation therapy were statistically significant independent factors.[12] In 2009, Gil et al reviewed complications after CFR based on time period, comparing CFRs performed from 1973 to 1995 versus 1996 to 2005. The authors found that complication rates were decreasing over the past 10 years due to a decline in wound infections. This decline was attributed to the introduction of improved broad-spectrum antibiotics in the perioperative period.[4]

In an international collaborative study, Ganly et al reviewed 1093 patients from 17 institutions who underwent anterior CFR. In their analysis of the data, there were 56 deaths (4.7%) and overall 433 postoperative complications (36.3%). They concluded that medical comorbidity, prior radiation therapy, and the extent of intracranial tumor involvement were independent predictors of postoperative complications.[5]

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Table 4 Factors associated with early and delayed complications

Variable (total)	Early Complications (%)	*p* value	Delayed complications (%)	*p* value	Delayed orbital complications (%)	*p* value	Delayed wound complications (%)	*p* value	Delayed brain complications (%)	*p* value
Age, y										
< 50 (13 patients)	5 (38.5)	0.77	7 (53.8)	0.67	4 (30.8)	0.28	3 (23.1)	0.63	2 (15.4)	0.77
>50 (18 patients)	6 (33.3)		10 (55.6)		9 (50.0)		3 (16.7)		2 (11.1)	
Gender										
Male (21 patients)	7 (33.3)	0.72	12 (57.1)	0.53	9 (42.9)	0.53	4 (19.0)	0.95	2 (9.5)	0.43
Female (10 patients)	4 (40.0)		5 (50.0)		4 (40.0)		2 (20.0)		2 (20.0)	
Orbital invasion										
No (28 patients)	9 (32.1)	0.93	15 (53.6)	0.75	12 (42.9)	0.75	5 (17.9)	0.55	3 (10.7)	0.33
Yes (3 patients)	1 (33.3)		2 (66.7)		1 (33.3)		1 (33.3)		1 (33.3)	
Brain involvement										
No (23 patients)	8 (34.8)	0.46	12 (52.2)	0.25	10 (43.5)	0.59	4 (17.4)	0.65	3 (13.0)	0.97
Yes (8 patients)	2 (25)		5 (62.5)		3 (37.5)		2 (25.0)		1 (12.5)	
Radiation										
No (3 patients)	1 (33.3)	0.93	1(33.3)	0.75	0 (0)	0.06	0 (0)	0.54	1 (33.3)	0.33
Yes (28 patients)	9 (32.1)		16 (57.1)		13 (46.4)		6 (21.4)		3 (10.7)	
Chemotherapy										
No (20 patients)	5 (25.0)	0.10	10 (50.0)	0.64	8 (40.0)	0.77	2 (10.0)	0.42	3 (15.0)	0.63
Yes (11 patients)	6 (54.5)		7 (63.6)		5 (45.5)		4 (36.4)		1 (9.1)	

Not significant = $p > 0.05$.

Our series of 31 consecutive patients undergoing CFR for anterior skull base malignancies revealed early and delayed complication rates of 35.5% and 54.8%, respectively. The overall rate of early complications was consistent with that reported in the literature. Interestingly, the incidence of late complications after treatment for anterior skull base malignancies is not well reported. In our series, the most common delayed complications were orbital (most commonly epiphora) and wound breakdown (nasocutaneous fistula). Although none of the variables examined in this study achieved independent statistical significance, there was a trend toward statistical significance in patients receiving adjuvant chemotherapy and radiation therapy in the delayed complication group, suggesting the effects of these treatments may manifest several months or even years after treatment completion. This highlights the importance of long-term follow-up for these patients because complications might not be immediately apparent.

The most common delayed orbital complication in this series was epiphora, with a rate of 22.5% (7 of 31 patients). Epiphora has been reported as one of the most frequent postoperative complications following anterior CFR with a reported rate of 36%.[14] Intraoperative management of the nasolacrimal system during maxillectomy varies, and options include simple transection, stenting, and marsupialization. Marsupialization, as performed in this series, has been reported to have a low rate of postoperative epiphora. Habib and Har-El reported their experience with 212 patients who underwent marsupialization of the nasolacrimal system at the time of maxillectomy (this included patients undergoing medial maxillectomy, complete maxillectomy, suprastructure maxillectomy, and anterior CFR). Their rate of postoperative epiphora was quite low, at 1.9%. However, the patient population is slightly different, in that not all patients underwent CFR and only 61 of 212 patients received radiation therapy. In addition, this study was addressing postoperative epiphora that did not resolve within 6 months of completion of treatment. In our study, epiphora often did not occur in the early postoperative period but was noted to develop at least 6 months after the completion of treatment. This underscores the need for continued monitoring and reporting of complications that occur in a delayed fashion.[15]

Nasocutaneous fistula has not been frequently reported in the literature as a complication after CFR specifically. However, data can be extrapolated from experiences with the management of paranasal sinus tumors. Paulino et al reported a 10.4% risk (5 of 48 patients) in patients undergoing surgical resection of maxillary sinus malignancy followed by radiation therapy.[16] Our significant rate (16.1%) of delayed posttreatment nasocutaneous fistula (5 of 31 patients) raises one potential advantage of endoscopic anterior CFR because a facial incision is avoided. In previously reported literature from this institution, Cianchetti et al reported a higher fistula rate in patients who had a transfacial incision compared with the overall group of patients undergoing treatment for advanced sinonasal cancer (15% versus 10%).[17] It seems reasonable to hypothesize that the adaptation of a purely endoscopic approach would lead to a decreased rate of nasocutaneous fistula. However, given the anterior tumor extension (and the need for partial nasal bone resection) in these patients, endoscopic resection was not considered feasible. Because of this experience, the management plan for patients that require extensive resection of the nasal bone or overlying skin/soft tissue envelope has been altered. In these patients, upfront free flap reconstruction of the skull base defect with concomitant reconstruction of the external defect is now pursued. Continued follow-up of this patient cohort will determine whether the complication of nasocutaneous fistula can be avoided with this change in reconstruction technique.

This study had several limitations. The study consisted of only 31 patients, the design of the study was retrospective, and several surgeons were involved. However, this observational study does highlight the risk of complications occurring several months to years after treatment, which is not frequently reported.

Conclusions

Anterior CFR remains a safe and effective procedure for treatment of anterior skull base malignancies. However, even with advances in surgery and reconstruction, both early and delayed complications of therapy continue to exist. These complications often affect quality of life several months to years after completion of overall treatment. This emphasizes the importance of long-term follow-up of patients with anterior skull base malignancies and the need for vigilance in the identification of delayed complications.

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