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Comparison of Transnasal Endoscopic and Open Craniofacial Resection for Malignant Tumors of the Anterior Skull Base

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Objective/Hypothesis: Craniofacial resection (CFR) represents the traditional approach for resection of anterior skull base (ASB) malignancies. However, this past decade has witnessed the emergence of transnasal endoscopic ASB resection (TER) as a feasible alternative. The aim of this study was to compare TER and CFR for ASB malignancy resection.

Methods: Retrospective analysis at a tertiary care medical center on 66 patients undergoing ASB malignant tumor resection between September 1997 and December 2006.

Results: Eighteen patients were treated with TER, whereas 48 patients underwent CFR. The two groups showed no significant difference in complication rate (27.8% for TER and 25.0% for CFR, $P > 0.05$), survival (94.4% for TER and 83.3% for CFR, $P > .05$), and metastasis (11.1% for TER and 8.3% for CFR, $P > .05$). A significant difference was observed in hospital stay with an average of 3.8 days in the TER group compared to 8.1 days in the CFR group ($P < .05$). Local recurrence approximated significance (5.6% for TER and 29.2% for CFR, $P = .051$)

Conclusions: TER of ASB malignancy is associated with a decreased hospital stay and faster recovery when compared to open CFR. Lower local recurrence rate in the TER group may reflect a discrepancy in histology and clinical stage. We found no significant differences in survival, metastatic, or complication rates in the two groups, whereas patients in the TER group had the added benefit of a desirable cosmetic outcome. Overall, TER seems to be an excellent alternative to CFR in properly selected cases.

Key Words: Transnasal endoscopic resection, craniofacial resection, anterior skull base, craniofacial, endoscopic, skull, base, transnasal, anterior skull base tumors, craniofacial resection, endoscopic anterior skull base resection.

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INTRODUCTION

Traditionally, anterior skull base (ASB) malignancies were treated with a craniofacial resection (CFR) (combining a bifrontal craniotomy with a transfacial approach) with the addition of postoperative radiation with or without chemotherapy.[1–4] This approach was considered the gold standard for treatment of anterior skull base tumors, and represented a major advance when described by Ketchum in 1963.[5] Recurrence rates were dramatically reduced by the resection of the cribriform plate. Nonetheless, this approach was associated with a significantly longer recovery time, and potential for major morbidity due to edema from brain retraction and removal and replacement of cranial bone as a free graft.[6] Many studies have reported major postoperative complications rates as high as 40%, and postoperative mortality approximating 5% after a CFR.[1,7–9] In addition to high morbidity and mortality associated with CFR, many additional factors have affected this algorithm. First, the belief that en bloc resection is routinely achieved with CFR was questioned by many experts.[10–12] In fact, one can effectively argue that skull base tumors resected via this approach in this complicated anatomic region often require piecemeal resection to clear margins, a fact that limits the en bloc resection argument as an advantage to CFR. Second, the notion that en bloc resection provides any oncologic advantage has never been proven. Many recent studies strongly support the idea that achieving true negative surgical margins is significantly more important than the manner in which a tumor is removed (en bloc vs. piecemeal resection).[8] Third, proponents of CFR argue that large anterior

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cranial defects cannot be safely repaired endoscopically. Techniques have now been developed to achieve safe endoscopic repair of large anterior skull base defects.[13]

The continuous advances in endoscopic surgical instrumentation, intraoperative image guidance, and optical aids have led to major improvements in endoscopic skull base surgery and made transnasal endoscopic resection (TER) a viable alternative to CFR. The last decade has witnessed the continuous progression of endoscopic skull base surgery from endoscopic resection of benign sinonasal tumors,[14] to endoscopic-assisted CFR,[10,15,16] to en bloc resection of sinonasal malignancy purely endoscopically.[17–26]

The purpose of this study is to 1) assess the morbidity and mortality of standard CFR and TER for malignant tumors of the anterior skull base; 2) compare the recurrence, metastatic, and survival rates of these two surgical approaches; and 3) determine the limitations of TER for anterior skull base malignancies.

MATERIALS AND METHODS

Experimental Design

A retrospective chart analysis was conducted to identify patients undergoing resection of malignant ASB tumors between September 1997 and December 2006 at the University of Miami/Jackson Memorial Medical Center. Records were evaluated for patient age, sex, diagnosis, tumor staging, histopathologic findings, operative procedure, operative time, estimated blood loss, complications, hospital stay, intensive care unit (ICU) stay, postoperative course, follow-up, recurrence rates, metastasis, and mortality. Olfactory neuroblastomas were staged according to the Kadish staging system.[27] Other malignant tumors were staged according to the tumor, node, and metastases (TNM) staging system for nasal cavity and ethmoid sinus malignancy of the sixth edition of the American Joint Committee on Cancer (AJCC).[28] Staging was based on preoperative examination, computed tomography (CT), magnetic resonance imaging (MRI), and surgical and pathologic reports. All patients included in this study underwent TER or CFR for curative intent. Patients with tumors deemed unresectable, who underwent palliative resection or debulking procedure, were excluded from this analysis. Skull base resections not including resection of the cribriform plate were also excluded. The protocol for this study was reviewed and approved by the institutional review board of the University of Miami, Miami, Florida.

Statistical Methods

Statistical comparison between the TER and CFR groups was performed using Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Survival was estimated using the Kaplan-Meier method. All tests were two-tailed and significance level was set at $P < .05$. All analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL).

Surgical Procedure

All tumors in the TER group were resected with an endoscopic approach alone, without external incisions, as described previously by Casiano et al.[12,20,26] Anterior skull base defects were reconstructed with lyophilized dura and mucosal grafts early in the study period, and acellular dermal allograft/Alloderm (LifeCell Corporation, Branchburg, NJ), a layer of Gelfoam (Pharmacia, Kalamazoo, MI), and Merocel tampons (Medtronic-Xomed, Jacksonville, FL) in the latter part of the study. Endoscopic procedures were performed by the senior author. Open ASB resection were performed by one of two very experienced head and neck oncologists with the assistance of a neurosurgeon via the standard CFR approach, and if needed additional transfacial access.[5] CFRs avoided facial incisions in all cases without skin or soft tissue involvement (coronal incisions with a basal, transnasal, or facial degloving approach). Reconstruction in that group was performed either by a pericranial flap, microvascular free tissue transfer, or a combination of the above.

RESULTS

Demographic Data

Sixty-six patients (39 males, 27 females) underwent ASB resection for malignant tumors during the study period with an overall mean age of 62.3 (range, 35–87 years). The mean age was 61.2 years (range, 39–81 years) for patients in the TER group, and 62.7 years (range, 35–87 years) in the CFR group ($P > .05$). The TER group was 44.4% female, compared to 39.6% in the CFR group ($P > .05$). Overall, 59.1% of the patients had significant medical comorbidities, 72.2% and 54.2% in the TER and CFR groups, respectively ($P > 0.05$). The mean follow-up was 31.7 months (range, 1–120 months) in the TER group, compared to 27.7 (range, 3–95 months) in the CFR group ($P > .05$).

Tumor Characteristics

Tumor histology and characteristics are listed in Table I. Squamous cell carcinoma was the most common pathology overall occurring in 37.9% of patients, followed by olfactory neuroblastoma (21.2%), and adenoid cystic carcinoma (16.7%). Squamous cell carcinoma (52.1%) was the most common pathology in the CFR group, whereas olfactory neuroblastoma (55.6%) was the most common in the TER group. Of the 10 patients with olfactory neuroblastoma in the TER group, five (27.8%)

TABLE I.
Tumor Histology.

Tumor Histology	TER	CFR	Total
Squamous cell carcinoma	—	25	25
Olfactory neuroblastoma	10	4	14
Adenoid cystic carcinoma	3	8	11
Adenocarcinoma	—	4	4
SNUC	1	2	3
Hemangiopericytoma	3	—	3
SNMM	—	2	2
High grade sarcoma	—	2	2
Small cell carcinoma	1	—	1
Basal cell carcinoma	—	1	1
Total	18	48	66

TER = transnasal endoscopic resection; CFR = craniofacial resection; SNUC = sinonasal undifferentiated carcinoma; SNMM = sinonasal mucosal melanoma.

TABLE II.
Tumor Staging.

Staging	TER, No. of Patients (% of Group)	CFR, No. of Patients (% of Group)	*P* (Fisher Exact Test)
Kadish A (OFN)	5 (27.8)	0 (0)	.001*
Kadish B (OFN)	2 (11.1)	0 (0)	.071
Kadish C	3 (16.7)	4 (8.3)	.380
TNM stage I	2 (11.1)	3 (6.3)	.608
TNM stage II	1 (5.6)	2 (4.2)	1.000
TNM stage III	3 (16.7)	10 (20.8)	1.000
TNM stage IV	2 (11.1)	29 (60.4)	<.001*

TER = transnasal endoscopic resection; CFR = craniofacial resection; OFN = olfactory neuroblastoma.
*Statistically significant.

were classified as Kadish stage A, two (11.1%) as stage B, and three (16.7%) were stage C. The four patients (8.3%) with olfactory neuroblastoma in the CFR group were all stage C. There were no stage A or B olfactory neuroblastoma in the CFR group. Whereas only two patients (11.1%) were stage IV (TNM classification) in the TER group, 29 patients (60.4%) were stage IV in the CFR group. This finding was statistically significant ($P < .001$). Table II illustrates the Kadish and TNM classification for the two groups of patients.

Operative and Perioperative Data

The operative and perioperative data for the two groups are illustrated in Table III. The mean length of hospital stay was 3.8 days (median, 3.5 days; range, 2–8 days) in the TER group, and was significantly shorter when compared to the CFR group (mean 8.1; median 7 days; range, 3–46 days) ($P < .001$). Similarly, patients who underwent TER enjoyed a shorter ICU admission ($P < .001$). We also found a significant decreased in operative time favoring the TER group with an average time of 271.8 minutes (median, 261.5; range, 155–512 minutes) in this group compared to 619.5 minutes (median, 625.5; range, 341–838 minutes) in the CFR group ($P < .001$). The estimated blood loss (EBL) was more elevated in the CFR group, with a mean EBL of 1075.0 mL (median, 1000; range, 400–3000 mL) compared to a mean EBL of 870.3 mL (median 825.0; range, 50–1700 mL) in the TER group, but did not reach statistical significance ($P > .05$). This resulted in a slightly higher percentage of transfusion in the CFR group, 29.2% compared to 22.2% in the TER patients without statistical significance ($P > .05$). Perioperative complications occurred in 5/18 (27.8%) patients in the TER group and 12/48 (25.0%) patients in the CFR ($P > .05$) (Table IV).

Recurrence, Metastasis, and Mortality

One patient (5.6%) in the TER group with stage II adenoid cystic carcinoma of the ethmoid region recurred locally despite postoperative radiation therapy. He was treated with aggressive revision endoscopic resection and is currently free of disease. The recurrence rate for the CFR group was 29.2% (14/48). One of the patients in that group had a T1 mucosal melanoma that recurred locally and metastasized to the ipsilateral neck. Another patient had a Kadish stage C olfactory neuroblastoma with extensive intracranial extension at presentation, with post-treatment local recurrence and neck metastasis. One patient with a T4N0M0 sinonasal undifferentiated carcinoma (SNUC) recurred locally. Two patients had local recurrence of high-grade chondrosarcomas. One patient with locally advanced adenoid cystic

TABLE III.
Overall Perioperative Data (N = 66).

Parameter	TER Median (Range)	CFR Median (Range)	*P*
Age, y	61.0 (39–81)	62.5 (35–87)	.735
OR time, min	261.5 (155–512)	625.5 (303–838)	<.001*
EBL, mL	825.0 (50–1,700)	1000.0 (400–3,000)	.060
ICU stay, d	0.0 (0–2)	3.0 (0–46)	<.001*
Hospital stay, d	3.5 (2–8)	7.0 (3–46)	<.001*
Follow-up, mo	26.0 (1–120)	24.5 (3–95)	.076
	TER Frequency (%)	CFR Frequency (%)	
Comorbidities	13/18 (72.2)	26/48 (54.2)	.263†
Transfusion rate	4/18 (22.2)	14/48 (29.2)	.759†
Complication rate	5/18 (27.8)	12/48 (25.0)	1.000†
Recurrence	1/18 (5.6)	14/48 (29.2)	.051†
Metastasis	2/18 (11.1)	4/48 (8.3)	.661†
Mortality	1/18 (5.6)	8/48 (16.7)	.425†
Radiation (postoperative)	14/18 (77.8)	44/48 (91.7)	.199†
Chemoradiation (postoperative)	2/18 (11.1)	16/48 (33.3)	.119†

TER = transnasal endoscopic resection; CFR = craniofacial resection; OR = operating room; EBL = estimated blood loss; ICU = intensive care unit.
*Indicates significance.
†Fisher exact test (all other *P* values were performed using Wilcoxon rank sum test).

TABLE IV.
Complications.

Complication	TER (No. of Patients)	CFR (No. of Patients)
Cerebrospinal fluid leakage	1	3
Diplopia	—	3
Epistaxis	2	—
Altered mental status	1	—
Vestibular stenosis	1	—
Epidural hematoma	—	1
Conjunctival tear	—	1
Ipsilateral blindness	—	1
Ectropion	—	1
Wound dehiscence	—	1
Sepsis/pneumonia	—	1

TER = transnasal endoscopic resection; CFR = craniofacial resection.

carcinoma also recurred locally. The remaining eight patients were all stage IV squamous cell carcinoma with intracranial and pterygoid fossa/plate extension. The difference in recurrence favored the TER as expected, given the differences in histology and stage, but failed short of statistical significance ($P = .051$).

Metastasis occurred in two patients in the TER group. One of these patients had ipsilateral temporal bone and neck metastasis from a stage III SNUC, whereas the other had an eyelid metastasis from a recurrent Kadish C olfactory neuroblastoma. Metastasis occurred in four patients in the CFR group. One patient with locally advanced (stage IV) squamous cell carcinoma metastasized to the ipsilateral parietal lobe. Another patient with advanced squamous cell carcinoma had local recurrence and neck metastasis. The other two metastases are the patient with early mucosal melanoma with local and neck metastasis, and the Kadish C olfactory neuroblastoma mentioned earlier. No significant difference in metastasis rate was found between the two groups ($P > .05$).

Figure 1 illustrates the survival curves for the two groups. The mortality rate was higher in the CFR group 8/48 (16.7%) when compared to the TER group 1/18 (5.6%), without statistical significance ($P > .05$). The only mortality in the latter group occurred in the patient with metastatic SNUC. The eight mortalities occurring in the CFR group were all in patients with extensive stage IV lesions. Seven of these patients had local recurrence, and one patient had distant metastasis without local disease.

Subgroup analyses were conducted for any pathology or stage with at least one patient in each group (Table V). Comparison of olfactory neuroblastomas showed a significant decrease in operative time, ICU stay, and hospital stay favoring the TER group. Comparison of adenoid cystic carcinoma between these two approaches showed a decreased operative time, EBL, and ICU stay, also favoring the TER group. No significant difference was observed for SNUC comparison. Analysis of Kadish C patients showed a significant decrease in operative time in the TER group. Patients with early stage disease (stage I or stage II) showed no differences when the two groups were compared. Similar to the Kadish C subgroup, patients with stage III disease had a significantly shorter operative time. Stage IV subgroup analysis showed a significant decrease in operative time, ICU stay, and hospital stay when TER was performed.

DISCUSSION

Surgical management of ASB malignancy is traditionally performed with a CFR. When combined with postoperative radiation with or without chemotherapy, this technique has shown a positive impact on treatment results of paranasal sinus malignancies extending to the anterior cranial fossa. As such, CFR has remained the gold standard for ASB tumor resection for nearly 50 years.[1–4] Nevertheless, CFR is associated with significant perioperative morbidity, mortality, and complications.[1,6–8] These limitations have prompted the search for more efficacious and safer approaches to the anterior cranial vault. Over the past decade, many endoscopic skull base surgeons have adopted TER for benign sinonasal tumors, and have found this approach to be safe and efficient when compared to CFR.[14] The significant improvement in visualization noted with this approach led to the development of endoscopic-assisted CFR for malignant sinonasal tumors.[9] As endoscopic skull base surgeons became more familiar with the endoscopic endonasal anatomy, small malignant tumors were resected successfully with this technique.[6] In 2001, Casiano described a purely endoscopic anterior skull base resection for olfactory neuroblastoma.[19] Since that time, many small case series have reported comparable oncologic results when TER is compared to CFR for

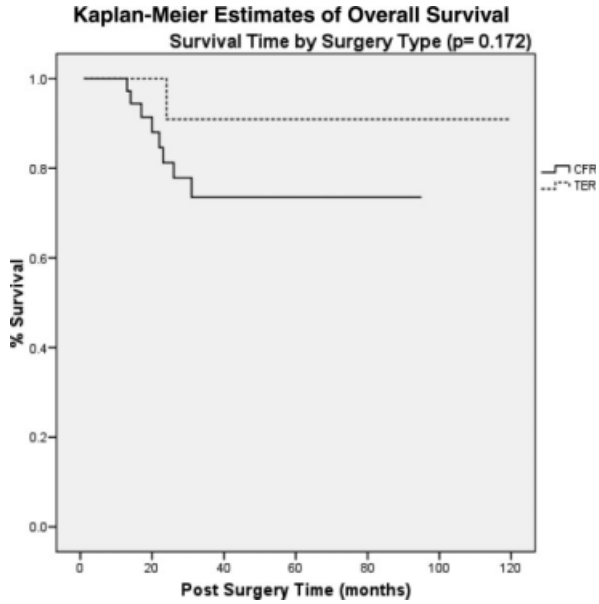

Fig. 1. Survival time (months) by surgical approach (broken curve, transnasal endoscopic resection; solid curve, craniofacial resection).

TABLE V.
P Values for Subgroup Comparisons (TER vs. CFR).

Parameter	OFN	ACC	SNUC	Kadish C	Stage I	Stage II	Stage III	Stage IV
Age	.524	.412	.221	.368	.248	.221	.127	.260
OR time	.005*	.024*	.221	.034†	.083	.221	.028*	.024*
EBL	.887	.024*	.221	.467	.236	.221	.390	.321
ICU stay	.002*	.048*	.221	.064	.197	.157	.059	.018*
Hospital stay	.007*	.345	.221	.077	1.000	.157	.433	.028*
Follow-up	.888	.215	1.000	1.000	.564	1.000	.932	.243
Comorbidities	1.000†	1.000†	—†	1.000†	.400†	—†	1.000†	1.000†
Transfusion	.520†	.491†	1.000†	.429†	—†	—†	.510†	1.000†
Complication	.095†	.273†	.333†	.486†	.400†	—†	.203†	1.000†
Recurrence	.286†	.491†	1.000†	1.000†	1.000†	.333†	—†	.510†
Metastasis	.505†	—†	.333†	1.000†	1.000†	—†	.231†	1.000†
Mortality	—†	—†	.333†	—†	—†	—†	.231†	1.000†
Radiation	1.000†	—†	—†	.429†	1.000†	.333†	.231†	.127†
Chemoradiation	.066†	1.000†	.333†	.429†	—†	—†	.423†	1.000†

TER = transnasal endoscopic resection; CFR = craniofacial resection; OFN = olfactory neuroblastoma; ACC = adenoid cystic carcinoma; SNUC = sinonasal undifferentiated carcinoma; OR = operating room; EBL = estimated blood loss; ICU = intensive care unit.

*Statistically significant.

†Fisher exact test (all other *P* values were performed using Wilcoxon rank sum test).

small, carefully selected anterior skull base malignancies.[6,17–19,21–26]

With the continuous advances in surgical instrumentation, optical aids, and image guidance, TER has evolved as a viable alternative to CFR for select malignancies. Advantages of this approach include superior visualization of difficult areas, such as the frontal recess, sphenoid sinus, orbital apex, pterygomaxillary space, and inferior part of the septum. This allows accurate resection of the tumor while sparing uninvolved vital structures. An additional benefit is the lack of external incisions and improved cosmesis. Despite these advantages, concerns have been raised regarding the safety and efficiency of this technique. One important issue is the feasibility of en bloc resection through this route, whereas some considered repairing a large anterior skull base defect endonasally to be inadequate. Many experts questioned the safety of reconstructing a large skull base defect with free nonvascularized grafts. Proponents of TER believe en bloc resection is rarely achieved with open CFR due to the anatomic limitations posed by this region, and consequently does not represent a disadvantage to TER. Furthermore, safe and successful large anterior skull base repairs have been described with many different techniques.[11,19,25]

In this study, our main goal was to compare the morbidity and complications associated with each group. Secondary objectives were to assess the recurrence, metastatic, and survival rates between the two approaches. Lastly, we evaluated the limitations of TER for resection of anterior skull base malignancy.

Complications rates were similar between the two groups (Table IV). The most common complication was cerebrospinal fluid leakage which occurred in three patients undergoing CFR, and one patient with a TER for recurrent olfactory neuroblastoma. Three patients in the CFR group had persistent postoperative diplopia, whereas two patients in the TER group necessitated postoperative nasal packing for control of epistaxis.

The EBL was considerably higher in the CFR group, although not statistically significant. This finding can primarily be explained by the significantly increased operative time observed in the CFR group, which translated into longer periods of blood loss, but also by the greater stage in the CFR group and potential issues related to the internal maxillary and carotid arteries. Furthermore, patients usually experience a significant amount of blood loss at the time of osteotomies for tumor removal during CFR. During that time, most surgeons concentrate on proper osteotomy positioning to prevent complications or incomplete tumor removal and accept a certain level of blood loss through the nasal cavity. This is different from a TER, where visualization is paramount and depends on meticulous hemostasis. As expected, the higher EBL found on the CFR group translated into a relatively higher percentage of transfusions in these patients. Nonetheless, this observation did not reach statistical significance.

We found no significant differences in metastatic and survival rates between the two groups. Although the Kaplan-Meier curves showed a slight improvement in 5-year survival favoring the TER group, this finding was far from reaching statistical significance (Fig. 1). Also, given the differences in stage and histology, it is difficult to reach definitive conclusions. Conversely, the rate of recurrence was much higher in the CFR group, and was close to reaching statistical significance ($P = .051$). This observation was likely due to the marked disparity in clinical stage, histology, and locally advanced disease between the groups. The CFR group had a significant and overwhelmingly higher percentage of stage IV disease (60.4% vs. 11.1%) and histologically more aggressive tumors (52.1% squamous cell carcinoma in the CFR group, compared to 55.6%

olfactory neuroblastomas in the TER group). This observation probably accounts for a large portion of the recurrences noted in this group. An alternative explanation for the difference in recurrence may be secondary to limited visualization around angles in the CFR group. Whereas the endoscopic approach allows clear visualization through different angled endoscopes, a CFR relies primarily on tactile discrimination, direct visualization, and preoperative anatomic imaging during tumor resection. The addition of intraoperative frozen section examination undoubtedly improves resection margins, but is only optimal when combined with adequate visualization. On the other hand, palpation is limited during TER.

Although care was taken to eliminate inaccuracies, this study is subject to limitations inherent in any retrospective study. One obvious limitation is that CFRs were performed by multiple surgeons, whereas the one surgeon performed all the TERs. Another important limitation is the significant stage and histologic disparity between the two groups. Whereas most of the endoscopic resections were performed on relatively well-selected, localized cases, most of the tumors in the CFR group were already at a locally advanced stage (60.4% stage IV). It is likely that less optimal results would have been achieved in the TER group if similar advanced disease was found in that group. One can argue that the higher recurrence rate observed in the CFR group is simply a reflection of the locally advanced nature of the disease in that group. In addition, it is important to note the short follow-up in the CFR group as a limitation to this study.

Based on our experience, we believe that in the hand of experienced and skilled endoscopic skull base surgeons, early and intermediate stage anterior skull base malignancies can be safely and successfully treated with TER while maintaining proper oncologic principles. This technique allows excellent visualization for tumor removal, and is associated with a faster recovery, decreased hospital stay, and arguably decreased local recurrence rates in selected cases, when compared to open CFR. Endoscopic-assisted CFR is an option for large tumors with marked intracranial, dermal, or orbital extension necessitating gross intracranial tumor resection, skin excision, or orbital exenteration, respectively. Open CFR is necessary for extensive tumors with skin and orbital extension not amenable to a purely endoscopic approach, and should be assisted with endoscopic equipment when appropriate to provide better visualization during tumor extirpation. Endoscopic skull base surgeons performing TER for malignancy should be familiar and proficient in performing CFR in case complete tumor extirpation cannot be achieved endoscopically, necessitating conversion to an open procedure. Similarly, surgeons who have a long experience in open CFR can incorporate endoscopic techniques into their armamentarium.

CONCLUSION

TER of anterior skull base tumors is associated with a decreased hospital and ICU stay, decreased EBL and transfusion rate, and faster recovery when compared to the traditional open CFR. Lower local recurrence rate in the TER group may reflect a difference in clinical stage, although we postulate that better visualization may be a factor in this outcome. We found no significant differences in survival, metastatic, and complication rates between the two groups, whereas patients in the TER group had the added benefit of a desirable cosmetic outcome. Overall, TER seems to be an excellent alternative to CFR in the hands of well-trained endoscopic skull base surgeons in properly selected cases. Additional large prospective and multi-institutional studies are needed to further evaluate this experience.

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