Technology in Cancer Research and Treatment
ISSN 1533-0346
Volume 9, Number 5, October 2010
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Combined Endoscopic Endonasal Surgery and Fractionated Stereotactic Radiosurgery (fSRS) for Complex Cranial Base Tumors—Early Clinical Outcomes

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Endoscopic endonasal surgery (EES) has been shown to be a feasible approach to cranial base tumors while reducing post-operative morbidity. Using the endoscopic endonasal approach alone or in combination with open approaches may provide advantages over conventional approaches. However, the balance between maximal resection and minimal injury to neurovascular structures frequently precludes gross total resection (GTR). Consequently, adjuvant radiation therapy may be an important option to improve local control (LC) of residual disease. In this retrospective series, we report clinical outcomes, morbidity, and LC of 40 patients with cranial base tumors treated with EES +/- combined open approach followed by fSRS (CyberKnife, Accuray Inc.). 26 patients had benign disease, 7 had newly diagnosed malignant disease, and 7 had previously resected malignant disease. Surgical outcomes were evaluable in all patients. LC after fSRS was evaluable in 39 patients and defined as no evidence of regrowth by MRI, CT, & physical examination. GTR was achieved in 12/40. Median post-operative length of stay (LOS) was 3 days. In multivariable analysis controlling for anatomic location and malignant histology, post-operative complications (n = 10) were significantly associated with patients having combined open and EES ($p < 0.01$, OR = 16.9). SRS was delivered in 1-5 sessions to a median marginal dose of 24.9 Gy. Median follow-up was 24.7 months (range, 1.5 to 61 months). LC was achieved in 89.7% (35/39) of evaluable patients. LC was achieved in 11/12 patients who had GTR. Median progression-free survival was 19.7 months (21.0 months for benign tumors (n = 26), 5.8 months for previously resected malignant disease (n = 7), and 21.2 months for newly diagnosed malignant disease (n = 7). Of the 31 patients who had symptomatic disease at presentation, 18 (58%) reported complete symptom resolution, 9 partial, and 4 no improvement. One patient who received two prior courses of radiation therapy developed osteosclerosis (grade III). Other adverse events were erythema (grade I, n = 5), nausea (grade II, n = 2), conjunctivitis (grade II, n = 1). EES followed by fSRS is a safe and effective management strategy for selected cranial base tumors. EES combined with an open surgical approach may result in increased complications. However, initial follow-up offers encouraging results indicating shorter time to recovery, acceptable LC rates compared to conventional approaches, and similar median time to progression for benign and newly diagnosed malignant disease.

Key words: Cranial base; Base of skull; CyberKnife; Endoscopic surgery; Stereotactic radiosurgery.

Abbreviations: fSRS: Fractionated stereotactic radiosurgery; EES: Endoscopic endonasal surgery; IMRT: Intensity modulated radiation therapy; BED: Biologically effective dose; GTR: Gross total resection; LC: local control; LOS: Length of stay; CFR: Craniofacial resection; EBRT: External beam radiation therapy.

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Introduction

The skull base includes portions of the anterior cranial fossa, clivus, petrous bone, middle cranial fossa, cavernous sinus and infratemporal fossa. It remains a challenging region to access via conventional surgical approaches that follow a lateral-to-medial trajectory. Approaches such as anterior transbasal (1, 2) and orbitozygomatic (3) were developed to provide access to midline tumors while reducing manipulation of critical and vulnerable neurovascular structures in this area. For pituitary adenomas, this region has been accessed via transphenoidal microsurgery for decades (4-7). However, efforts to improve surgical technique and outcomes have led to the development of endoscopic endonasal surgery (EES) as an alternative to microsurgery via sublabial or septal incisions (8). More recently, EES has been shown to be an effective alternative in the management of cranial base meningiomas (9) and chordomas (10) with greatly reduced post-operative hospital stays compared to conventional approaches to the cranial base (11, 12). Due to the close association of base of skull tumors with critical neurovascular structures, resection of lesions within or near the cavernous sinus, jugular foramen, petroclival and sellar regions has lead to complication rates as high as 40% (13-15). High complication rates (with past microsurgical approaches) combined with significant rates of recurrence have lead to increasing acceptance that optimal management for cranial base tumors is not operative removal alone (15-17). As a result, stereotactic radiosurgery has become an important adjuvant or primary treatment option for patients with tumors of the cranial base (18).

In previous years, concerns for potential toxicity from treatment of large volume lesions with single-fraction stereotactic radiosurgery (SRS) combined with technical limitations for the treatment of lesions close to the brain stem prevented the use of radiosurgery for many patients. For many of these patients, conventional fractionated radiotherapy or intensity-modulated radiotherapy (IMRT) was used instead (18). However, as radiosurgical technology has evolved, the use of SRS, defined as a high dose of externally generated ionizing radiation administered with the aid of stereotactic localization in one to five fractions (19), for base of skull tumors has increased due to several key advantages over conventional fractionated methods of radiation therapy (RT). The advantages are that fSRS appears to produce more tumor response than conventional fractionated methods (18), it has rapid dose-falloff which affords improved sparing of adjacent critical structures, and it presents added convenience for patients through shorter-treatment duration. The radiobiological advantages of large fraction sizes given over a shorter period of time may provide the basis for the differences observed when compared to conventional radiation therapy techniques (20).

Endoscopic endonasal resection followed by fSRS is a novel and appealing, minimally-invasive treatment combination for cranial base tumors due to reduced post-operative hospitalization compared to other operative techniques (8, 21). Furthermore, fSRS offers technical advantages over conventional radiation therapy. For large residual tumors, multi-session fSRS offers potential advantages compared to single-fraction SRS. The multi-session technique allows for a high dose per fraction, normal tissue recovery between fractions, and increased cell-kill from re-oxygenation may enhance local tumor control (22). The goals of adjuvant fSRS in this setting are long-term tumor growth prevention and preservation of neurological function.

Herein, we present the results of our clinical experience with EES followed by adjuvant single and multi-fraction SRS to manage benign and malignant tumors of the cranial base.

Patients and Methods

The clinical information of over 1900 patients treated with linear accelerator-based stereotactic radiosurgery between 2000 and the present is maintained in the University of Pittsburgh Cancer Institute, Institutional Review Board-approved database. A review of this database identified 40 patients with cranial base tumors that were treated with EES followed by adjuvant fractionated radiosurgery using the CyberKnife Robotic Radiosurgical system (Accuray, Inc, Sunnyvale, CA). Among these patients, 19 were men and 21 were female. The median age was 50 years (range: 22–85 years). Patient characteristics are summarized in Table I.

Patients included in this analysis were those with newly-diagnosed cranial base tumors treated with EEA and adjuvant fSRS and recurrent disease treated with EEA followed by fSRS. Eleven patients previously underwent at least one open surgical resection and 9 patients previously had EES, for a total of 23 operations. Three patients had prior SRS and 9 had other methods of external beam radiation therapy, including 2 who received proton therapy. Seven patients were treated with chemotherapy or biologic therapy prior to treatment with endoscopic endonasal surgery and adjuvant fSRS.

The decision to offer EES prior to fSRS was based on pathology, reasonable surgical access and most importantly, the presence of symptoms from mass effect or neurologic dysfunction. In general, the vast majority of patients referred to our center have significant neurological compromise including vision loss that would not respond to radiation alone and requires decompression. All cases were seen and discussed in a combined skull base tumor conference by surgeons, radiation oncologists and radiologists.

Table I
Patient Characteristics.

Characteristic	Number (Percentage)
Sex	
Female	21 (52.5)
Male	19 (47.5)
Age	
Median	50
Range	22–85
Tumor type	
Meningioma	13 (32.5)
Pituitary adenoma	8 (20)
Nasopharyngeal carcinoma	3 (7.5)
Glomus jugulare	3 (7.5)
Squamous	3 (7.5)
Adenocarcinoma	2 (5)
Chondrosarcoma	2 (5)
Adenoid Cystic Carcinoma	2 (5)
Adeno-squamous	1 (2.5)
Cavernous Hemangioma	1 (2.5)
Chondroma	1 (2.5)
Chordoma	1 (2.5)
Location	
Intracranial	16 (40)
Perioptic	13 (32.5)
Head and Neck	11 (27.5)
Previous Treatments	
Open Surgery	14
Endoscopic Surgery	9
Single Session SRS	2
Radiotherapy	9

Pathologic and Anatomic Characteristics

Tumors were classified based on location and histological diagnosis (Table I). For clarity of presentation and analysis, we classified the anatomic location of the tumors similarly to a prior series by Tuniz *et al.,* (23) into 3 groups: intracranial, perioptic, and head and neck. "Intracranial" lesions were located within the intracranial space but not adjacent to the anterior optic tract. "Perioptic" tumors were those with at least some portion involving or adjacent to the anterior optic tract. "Head and neck" tumors were located at the base of skull and posterior fossa extending to upper portions of the neck and upper cervical vertebrae, *i.e*. C2.

Endoscopic Endonasal Tumor Resection

Patients underwent operation via endoscopic endonasal techniques at the University of Pittsburgh Medical Center. For 7 patients, the best access to the tumor was achieved with a combination of endoscopic endonasal and open approaches. A two-stage operation was used in 16 of the 40 patients to achieve maximal resection. The surgical concepts and techniques of the procedure used at our center have been well described (24-27).

Frameless Stereotactic Radiosurgery

Patients were treated with the CyberKnife Robotic Radiosurgical System (Accuray Inc, Sunnyvale, CA), a 6-MV linear accelerator mounted on a 6-axis robotic arm. An individualized treatment plan was developed for each patient according to the clinical and radiographic findings. Contrast-enhanced, thin-slice high resolution CT imaging was performed in all patients using a GE Light Speed 8i or 16i scanner (General Electric, Milwaukee, WI). For some patients, CT imaging was supplemented with contrast-enhanced, fat suppressed thin-slice (2-mm) MRI. This combination provided excellent visualization of the cranial base lesions and the critical surrounding anatomy. The CT and MRI scans were fused using the CyberKnife treatment planning system. Treatment planning was aided by PET scan in 22 patients. The treating physician then contoured the target and surrounding critical anatomy from the treatment planning CT or from the composite CT/MRI. Treatment planning was conducted using a nonisocentric inverse planning algorithm. The gross tumor volume (GTV) and its margin were outlined with adjacent structure dose limitations to provide a planning target volume. Critical structures near the target were outlined to ensure an acceptably low dose. In cases of gross total resection (GTR), the radiation treatment plan was designed to the resection cavity, adjacent skull base dura, and bone. Therefore, the GTVs represent the volumes of the treated regions and were used to calculate the median and range of the tumor volumes.

The total dose to all critical structures other than the spinal cord, accounting for prior radiation therapy, was not routinely available in all patients because many were initially treated at outside institutions. For patients who were previously treated with radiation therapy but whose prior dose was unknown, we assumed a prior maximum dose of 50-60 Gy via conventional fractionated radiation therapy and planned the radiosurgical dose on that basis.

For all patients, dose and fractionation decisions were based on tumor pathology, volume, location, proximity to the brainstem and/or visual pathways, patient age and previous history of radiation therapy. For patients receiving multisession fSRS, dose selection was also shaped by the published literature on single-fraction radiosurgery (SRS) and on a calculated biologically effective dose (BED) using conventional fractionated radiotherapy as a point of reference. In general, critical structure constraints were as follows: spinal cord maximum dose: ≤8 Gy; larynx: ≤20 Gy; mandible: ≤20 Gy; parotid: variable; brainstem: ≤8 Gy; optical tract: ≤7 Gy; oral cavity: variable. Patients were treated to the ≥80% isodose line, which was intended to cover >90% of the target volume. The median post-operative tumor volume in this series was of 9.65 cm^3 (range: 0.64-103 cm^3). The median dose to the tumor margin was 22 Gy (range 15-50 Gy), median

maximum dose 28.25 Gy (range 17.5-61 Gy). Radiosurgery was delivered in 1 to 5 sessions (median: 3 sessions). Using an alpha/beta ratio of 3 for benign tumors and 10 for malignant, this is equivalent to median 54.3 Gy (range 42.2-88.0 Gy) and 48.0 Gy (range 22.5-100.0 Gy), respectively, of conventional radiotherapy delivered in 2 Gy fractions (Tables II and III). Representative CyberKnife treatment plans for a post-resection residual meningioma of the cranial base (Figure 1) and adenocarcinoma (Figure 2) are provided.

During treatment sessions, real-time imaging of the patient is acquired via 2 orthogonally placed radiographic cameras and compared with the treatment-planning CT. This allows for changes in patient position to be determined and for the radiation beam to be adjusted over multiple treatments without the use of an invasive stereotactic frame. For treatments of greater than one session, during each treatment, patients were repositioned to simulate the original treatment planning setup and the desired center of the treatment field was identified. The duration of each treatment session was approximately 45 minutes to one hour. Radiosurgery was routinely administered on an outpatient basis with an interfraction time of approximately 48 hours.

Follow-up evaluation including history, neurological examination, visual-field testing, and MRI was conducted at 6 month intervals for the first 2 years after treatment and at yearly intervals thereafter. Tumor volume was assessed by measuring the 3 largest dimensions (vertical, lateral, and anteroposterior) in the region of the pre-radiosurgical tumor enhancement. These values and the formula for an idealized ellipsoid volume (volume = $4/3\pi$[length/2 x width/2 x height/2]) were used to assess radiologic response over time and were scored as stable, smaller or larger. These values were compared to the electronically-determined absolute tumor volume from the treatment planning images.

Table II
Radiosurgical dosimetry.

Target volume (cm^3)	
Median	9.63
Range	0.64–103
Marginal dose (Gy)	
Median	22
Range	15–50
Maximal dose (Gy)	
Median	28.25
Range	17.5–61
BED_3	
Median	54.3
Range	42.2–88.0
BED_{10}	
Median	48.0
Range	22.5–100.0
Conformality Index (PIV/TIV)	
Median	1.32
Range	1.08–1.75
Modified conformality index (TIVxPIV)/TV	
Median	0.170
Range	0.014–2.73

BED, biologically effective dose; PIV, prescription isodose volume; TIV, target isodose volume; TV, target volume.

Table III
Pathologic and radiosurgical characteristics by anatomic group.

		Tumors	
Location and dosage	Values	Histology	No.
Head and Neck		Nasopharyngeal Ca.	3
Dosage		Glomus jugulare	2
Median BED (Gy)	53.8	Squamous	3
Range	10.3–66.6	Meningioma	1
Median fractions	5	Pituitary adenoma	1
		Adenoid Cyst. Ca.	1
Perioptic		Pituitary adenoma	5
Dosage		Meningioma	3
Median BED (Gy)	48.0	Chondrosarcoma	2
Range	33.3–78	Cavernous hemangioma	1
Median fractions	5	Adenocarcinoma	1
		Squamous	1
Intracranial		Meningioma	9
Dosage		Pituitary adenoma	2
Median BED (Gy)	53.8	Adenoid Cyst. Ca.	1
Range	22.5–88	Glomus jugulare	1
Median fractions	5	Adenocarcinoma	1
		Chondroma	1
		Chordoma	1

Statistical Analysis

Fisher exact test was used to compare possible relationships of categorical pre-treatment and treatment-related variables between the patients who had local failure and those who remained locally controlled throughout the duration of follow-up. Significant differences between the 2 groups were subsequently tested with logistic regression with stepwise addition. These analyses were repeated using post-operative complications and adverse events after fSRS as separate dependent variables. For continuous variables, univariate logistic regression was conducted followed by stepwise addition to multivariate logistic regression for covariates significant by univariate analysis.

Results

The median total follow-up in this series was 24.7 months (range: 0-58 months). Median follow-up stratified by benign vs. malignant disease was 25.1 months and 17.6 months, respectively. The median progression free survival was 19.8 months. The median progression-free survival stratified by benign vs. malignant tumor pathology was 21.0 months and

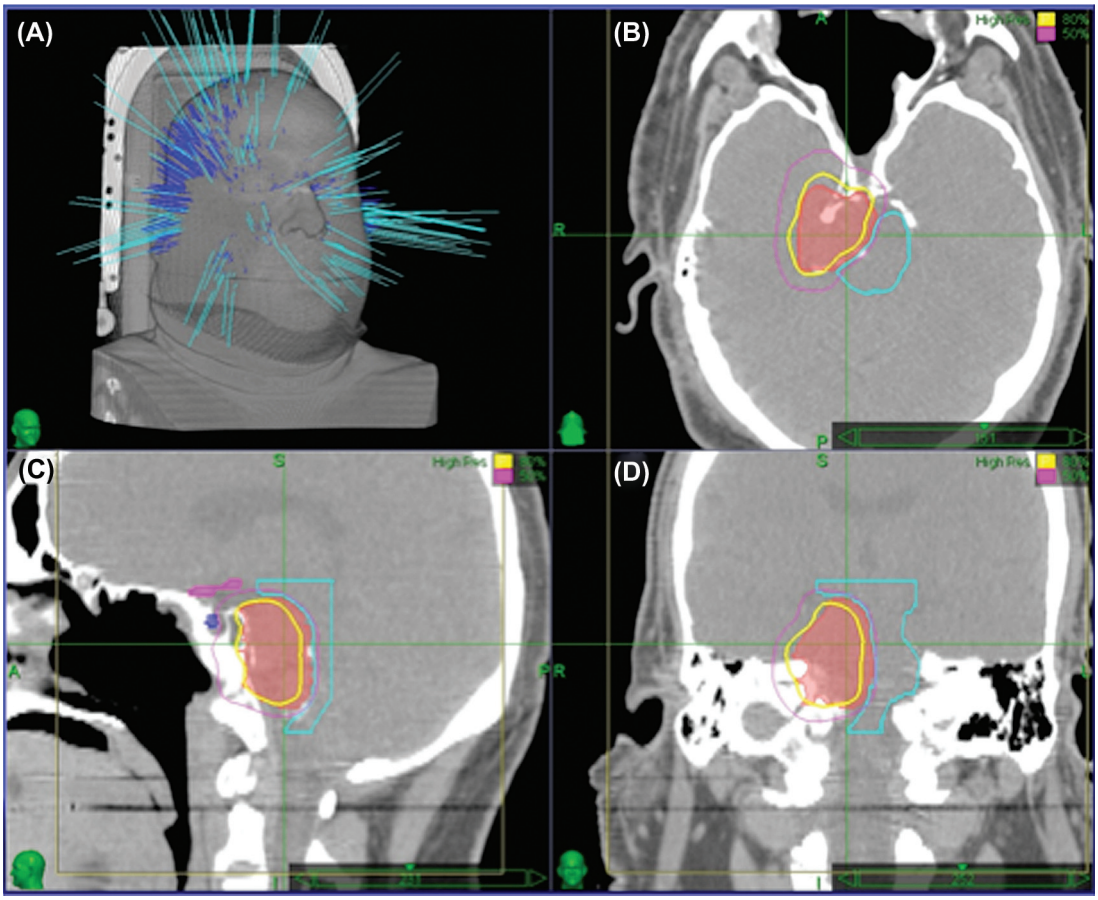

Figure 1: Axial Cyberknife treatment planning computed tomographic (CT) scan (**B**) with sagittal and coronal reconstructions (**C, D**) of a multisession SBRT of a petroclival meningioma in a 46 yo man. A marginal dose of 20 Gy was delivered to the 80% isodose line (Yellow) in 5 Sessions. A conformal dose gradient was achieved with 160 nonzero beams (**A**). The tumor volume was 16.1 cm^3. The conformality index was 1.26. The 50% isodose line (purple) is also pictured.

9.7 months, respectively. The separate progression-free survival curves (Kaplan-Meier) for patients with malignant or benign tumors are presented (Figure 3).

Gross total resection (GTR) was achieved in 12 of 40 patients (30%). Two patients had benign disease including a glomus tumor and a patient with WHO Grade I meningioma that was referred for SRS after routine radiological follow-up documented progression. GTR in this population was defined as no disease present on post-operative imaging. Ten patients had varying malignant histology's (3 nasopharyngeal carcinoma, 1 chondrosarcoma, 1 mixed adeno-squamous carcinoma, 1 chordoma, 2 squamous cell carcinomas and 2 adenoid cystic carcinomas). GTR was defined in the malignant cohort as no tumor visible on post-op imaging and clear margins in those cases involving carcinomas. Among these 12 patients, 11 underwent EES without a combined open approach.

Thirty-nine of 40 patients had radiologic follow-up after fSRS. At the first radiologic follow-up after fSRS (median: 96 days), 4 patients had progressive disease, all were malignancies (1 had nasopharyngeal carcinoma, 2 had adenocarcinoma and 1 had chordoma), and 35 of 39 (89.7%) had local control. Of the 12 gross totally resected tumors, 1 had progression at first radiologic follow-up after fSRS. The remaining 11 showed no evidence of regrowth. Of the 27 tumors with subtotal resection, 9 tumors (all benign) demonstrated a decrease in volume greater than 20%, 15 were stable, and 3 malignant tumors progressed locally (2 adenocarcinoma and 1 chordoma; Table IV). However, 10 of 35 patients who initially experienced local control later recurred locally. Seven of these 10 had malignant disease. Ten patients also experienced distant failure, 9 of which had malignant primary disease.

Benign Disease

Of the 40 patients in this series, 26 (65%) had benign histology. GTR was achieved in 3 of these 26. In 4 cases, EES was combined with an open approach. Post-operative complications occurred in 6 of 26 benign cases (23.1%), 2 of

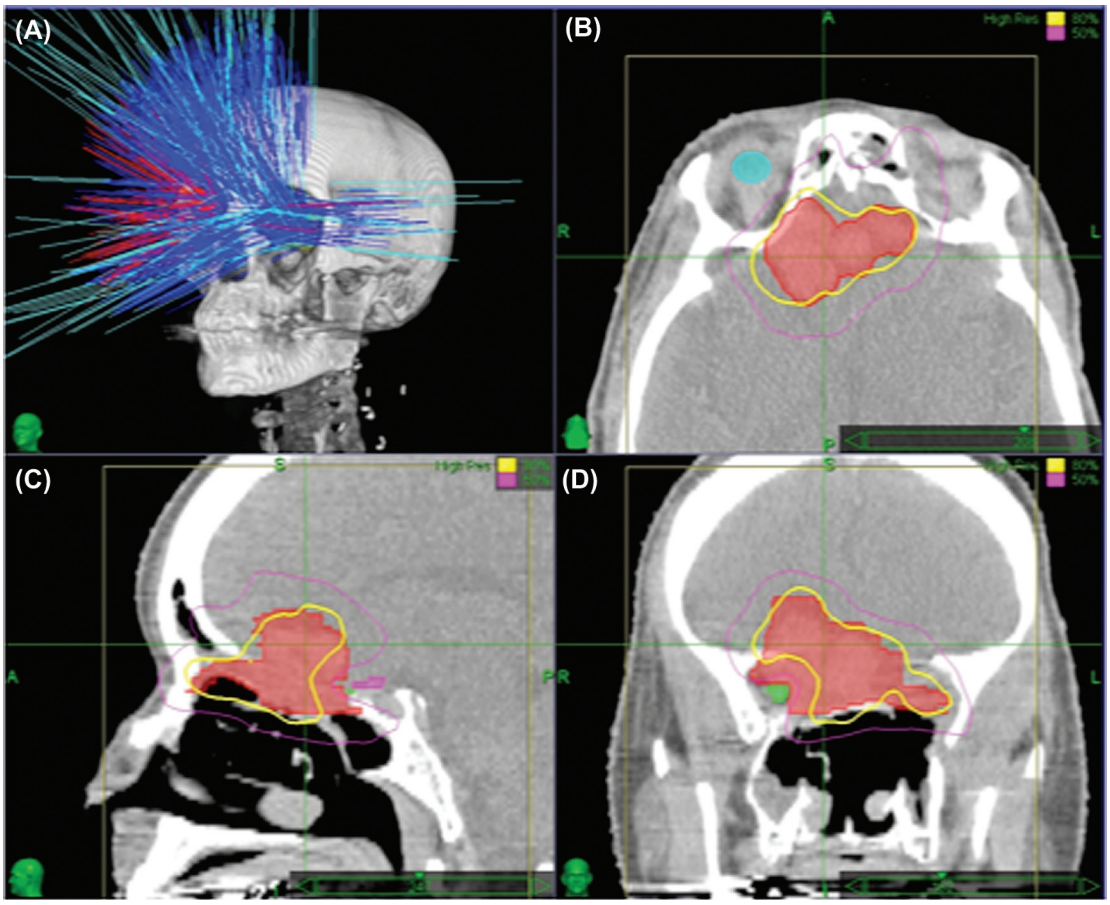

Figure 2: Axial Cyberknife treatment planning computed tomographic (CT) scan (**B**) with sagittal and coronal reconstructions (**C, D**) of a multisession SBRT of a sinonasal adenocarcinoma in a 41 yo woman. A marginal dose of 20 Gy was delivered to the 80% isodose line (yellow) in 3 sessions. A conformal dose gradient was achieved with 163 nonzero beams (**A**). The tumor volume was 31 cm^3. The conformality index was 1.32. The 50% isodose line (purple) is also pictured.

which employed combined open approach. Post-operative complications consisted of 3 cerebrospinal fluid (CSF) leaks requiring re-operation for repair, 1 hematoma requiring evacuation, 1 pulmonary embolus, and 1 patient developed hydrocephalus requiring VP shunt placement. Of the

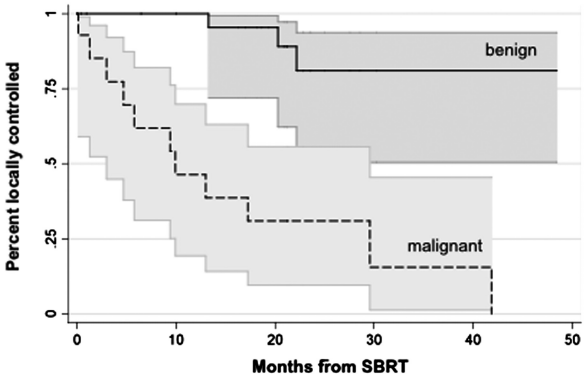

Figure 3: Kaplan-Meier analysis for local control with 95% confidence intervals stratified by benign/malignant histology.

26 patients with benign disease, 21 were symptomatic at the time of presentation. Fourteen of these had complete resolution of their symptoms following fSRS and 7 experienced partial improvement of their symptoms.

Malignant Disease

Fourteen of the 40 patients (35%) in this series had malignant disease. Seven patients were newly diagnosed and 7 had recurrent disease previously treated with at least one resection and were referred for a second resection for symptom palliation.

Among patients who previously underwent resection, 3 underwent EES combined with an open approach. GTR was achieved in 3 of the 7 recurrent cases, one of which required a combined open approach. Four patients with previously resected disease developed post-operative complications after EES, 3 of which had EES combined with an open approach. Post-operative complications in this subset included 1 CSF

Table IV
Radiologic outcomes after SRS by tumor pathology (N = 39).

Treatment radiologic outcome	Number (% of total)
Tumor volume decrease (≥ 20%)	9 (23.1)
Pituitary adenoma	4 (10.3)
Meningioma	3 (7.7)
Glomus jugulare	1 (2.6)
Cavernous hemangioma	1 (2.6)
Lesion volume stable*	26 (66.6)
Meningioma	10 (25.6)
Pituitary adenoma	4 (10.3)
Glomus jugulare	2 (5.1)
Squamous cell carcinoma	3 (7.7)
Nasopharyngeal carcinoma	2 (5.1)
Adenoid Cystic Carcinoma	2 (5.1)
Adeno-squamous	1 (2.6)
Chondrosarcoma	1 (2.6)
Chondroma	1 (2.6)
Progressive disease	4 (10.3)
Adenocarcinoma	2 (5.1)
Nasopharyngeal carcinoma	1 (2.6)
Chordoma	1 (2.6)
Chondrosarcoma	1 (2.6)

*Includes 10 gross total resections with no regrowth after SRS.

leak requiring re-operation for repair, 1 case of worsening pituitary function, 1 hematoma requiring evacuation, and 1 case of new-onset pain and numbness in the maxillary distribution of the trigeminal nerve which resolved 6 weeks after resection. Following adjuvant fSRS, the median progression free survival of these 7 patients was 5.8 months, including 2 patients who had progressive disease at the first radiologic follow-up, 4 who subsequently failed locally and 1 patient who had no radiologic follow-up. Three of the 4 patients with local failure also developed disease distantly. Of the 7 patients with malignant, previously resected disease, 5 were symptomatic at the time of presentation. Two patients had complete resolution of their symptoms following fSRS. Two others experienced a partial improvement and 1 patient experienced no improvement.

For the 7 patients with newly diagnosed malignant disease, all were resected with EEA without combined open approach. GTR was achieved in 6 of 7 cases. None of these seven patients developed a post-operative complication. Following fSRS, the median progression free survival was 21.2 months, including 2 patients who had progressive disease at the first radiologic follow-up, and 3 who subsequently failed locally. All 3 of these patients with subsequent local failure also developed disease distantly. Of the 7 patients with malignant, newly diagnosed disease, 5 were symptomatic at the time of presentation. Two patients had complete resolution of their symptoms following fSRS. Two others experienced a partial improvement and 1 patient experienced no improvement.

Local Failures

Malignant histology ($p < 0.01$), subtotal total resection ($p < 0.02$), prior radiation treatment ($p = 0.02$), and categorical tumor location ($p = 0.05$) were significantly associated with local failure. Age at SRS, tumor volume, prescribed dose, or recurrence versus newly diagnosed disease were not associated with the occurrence of local failure in this series (Table V). Logistic regression was used to evaluate the independent predictive value of those variables that were significantly associated with local recurrence. Using stepwise selection, only malignant histology remained in the final predictive model ($p < 0.01$, OR, 26.8; 95% CI, 3.70-194.1).

Post Operative Complications

The median post-operative length of hospital stay (LOS) was 3 days (range: 1–27 days). Similar LOS was seen in patients with benign disease and malignant disease (2.5 days, range: 1–18 and 3.0 days, range: 1–5, respectively). Patients with the longest LOS were those with post-operative complications requiring re-operation (n = 6). Combining the previously outlined subsets, the total number of patients who developed a post-operative complication was 10. The presence of surgical complications was significantly associated with the use of EES combined with an open approach (5/7) ($p < 0.01$, Fisher's exact test). The presence of surgical complications was not associated with any other covariate, including previous radiation therapy ($p = 0.14$), prior resection ($p = 0.22$) nor benign vs. malignant tumor histology ($p = 0.72$) or repeat resection of malignant disease ($p = 0.07$).

Morbidity following Fractionated Stereotactic Radiosurgery (fSRS)

Following fSRS, no patients experienced grade IV acute or late radiation toxicity by the RTOG radiation morbidity scoring criteria. One patient who was previously heavily treated with radiation, including conventional fractionated

Table V
Fisher exact test or univariate logistic regression comparing pre-treatment characteristics to local failure after initial radiologic response.

Characteristic	P value
*Malignant	0.001
*Subtotal resection	0.016
*Prior radiation	0.020
*Tumor location	0.05
Recurrence	0.3
°Tumor volume	0.5
°Prescribed dose	0.07
°Age at SRS	0.2

*Statistically significant.
°Univariate logistic regression.

radiation therapy and a prior course of SRS, developed grade III osteosclerosis. One patient developed grade III fatigue 3-5 weeks after fSRS. All other adverse events were mild (grade I) to moderate (grade II). Grade I erythema or desquamation occurred in 5 patients, 2 patients experienced grade II nausea, 1 patient developed grade II moderate conjunctivitis and 3 patients had grade I-II fatigue. No statistically significant relationship was found between adverse events after SRS and any treatment or pretreatment factors including prescribed dose, previous irradiation, other past treatments, or combined open surgical approach.

Late radiation morbidity documented on serial MRI scans showed increased T2 signal in the peri-tumoral brain without contrast enhancement in 3 patients at a median of 9 months after fSRS. This finding suggests radiation injury. These 3 patients all had sub-acute neurological worsening coincident with the appearance of these imaging changes. Their symptoms included seizure with headaches and cognitive worsening in 1 patient, headaches and cognitive worsening in 1 patient, and headache alone in the remaining patient. These symptoms resolved at a median interval of 3.5 months after onset. All 3 of these patients previously received radiation therapy. Two had prior conventional fractionated radiation therapy to 40 Gy and 50 Gy, respectively, and one had prior proton therapy to 75 Gy. No patients experienced new permanent cranial neuropathy following fSRS. However, three other patients developed ipsilateral facial spasms 3-6 months after SRS that improved with glucocorticoids and resolved within 2 months.

Discussion

Surgical resection has long been standard care for cranial base neoplasms. Tumors of the skull base have traditionally been managed with various open approaches to achieve satisfactory surgical exposure and tumor free margins. While these extensive approaches are curative in select patients, the high rate of complications that result from the manipulation of the surrounding neurovascular structures that these tumors often invade is a substantial drawback to these methods (11-15). Despite advances in surgical technique, postoperative mortality has remained as high as 9% (median, 3.6%) in series of open surgical resection of cranial base tumors (28-34). Furthermore, morbidity after open resection of cranial base meningiomas continues to be high. For example, the incidence of permanent cranial nerve deficits has been reported to be as high as 44%-56% (13-15, 35-37). In this setting, EES of cranial base tumors was developed.

This series of 40 patients represents only a subset of the EES of the skull base from the University of Pittsburgh that were referred for post-op SRS. EES achieved gross total resection (GTR) in a minority of cases. This was largely a reflection of planned pre-operative subtotal resection used as part of a combined strategy with SRS. This approach may reduce post-operative morbidity, and hospital stay compared to conventional approaches (9, 11 ,12). Median post-operative length of stay (LOS) was 3 days in our series, which presents an improvement compared to past series of craniotomy and extended anterior subcranial approaches (38-41). In a series of over 200 meningiomas treated with conventional approaches to the cranial base, median critical care unit stay was 5 days and medial overall post-operative LOS was 14 days (40). In a smaller series comparing endoscopic resection to traditional craniofacial resection (CFR), patients who underwent CFR had a median LOS of 7.17 days whereas those who underwent EES had median LOS of 5.24 days (38). However, a series of 60 patients comparing the anterior subcranial approach (CFR) to frontal craniotomy reported post-operative LOS of 4.0 and 7.0, respectively (41). The longer LOS seems to be reflected in the statistically significant increase in post-operative complications seen in the 7 patients in our series who had EES combined with an open approach.

The central motivation for following EES with adjuvant fSRS originates from reports of local progression after subtotal resection of even benign cranial base tumors. The progression rate of meningioma after subtotal resection without adjuvant radiation therapy has been reported to be as high as 70% (42). Another series of 38 partially resected meningiomas without adjuvant radiation reported a yearly growth rate of 4.94 cm^3/yr and a 5-year progression- free survival rate of 60% (43). By contrast, in a series of 140 patients with partially resected cranial base meningiomas treated with adjuvant conventional fractionated radiation therapy, Goldman *et al*., (44) reported 98% 5-year progression-free survival. The vast majority of series investigating adjuvant radiation therapy for cranial base tumors have been limited to meningiomas. However, the management principles conveyed by these series are, in general, followed for other benign cranial base tumors such as paragangliomas and schwannomas.

As expected, the median progression free survival of patients with benign cranial base tumors (21.0 months) was several months longer than that of patients with malignant cranial base tumors (9.7 months). However, stratification of patients with malignant disease by repeat resection for recurrent disease (n = 7) versus new diagnosis (n = 7) produces median progression free survivals of 5.8 and 21.2 months, respectively. In this series with relatively small numbers of patients in each subgroup, our results show that treatment with EES plus fSRS may produce similar progression free survival in benign and newly diagnosed malignant cranial base tumors. However, additional patients and follow-up are needed.

A variety of external beam radiation therapy (EBRT) techniques including single-session SRS, multi-session stereotactic radiation therapy (SRT), and conventional

fractionated schemes are available as a primary treatment option or as adjuvant treatment after resection of cranial base tumors. The choice of which technique utilized is in part influenced by patient age, functional status, medical comorbidities, and the anatomy of the disease. However, lesion size and location have a particularly important influence on the utility and efficacy of radiosurgery. As the volume of the target lesion increases, the volume of surrounding healthy brain and vasculature that is irradiated also increases. In addition, early generations of frame-based SRS techniques were not well-suited to tumors caudal to the foramen magnum. These limitations combined to restrict the use of SRS to smaller intracranial tumors. Larger cranial base lesions have more commonly been approached with open subtotal surgical resection followed by adjuvant radiosurgery or conventional RT to the residual disease.

The choice between fSRS/SRT or conventional fractionated radiation therapy after resection, endoscopic or open, has not been definitively addressed by a large prospective trial. However, the use of fSRS or SRT has gained favor in many centers. One possible explanation of this trend may be that the rapid dose fall off afforded by radiosurgical techniques allows greater sparing of brain and other critical surrounding organs than conventional fractionated RT. In addition, higher rates of local control with multi-session fSRS may be ascribed to the radiobiological advantage of large fraction sizes with increased cell kill due to reoxygenation in the interim between sessions (18, 20, 22).

The long-term sequelae of low-dose radiation delivered to surrounding healthy tissue at the cranial base via conventional EBRT techniques have not been well characterized. However, based on the single session SRS literature, the risk of secondary malignancy following conventional fractionated RT appears to be higher than after SRS (45, 46). Future series to elucidate the importance of this risk are called for, especially considering the long-life expectancy of many patients with benign cranial base tumors.

In this series of patients with a mixture of benign and malignant cranial base tumors, EES followed by fSRS generated from the CyberKnife Radiosurgical System appears to be safe and effective. Of the 10 patients who subsequently progressed locally after treatment plus the 4 who progressed immediately, 11 had lesions with malignant histology. It is possible that the median follow-up of 24.7 months for this series may be too limited to fully observe the natural history of the benign tumors. However, one series of over 1040 patients with meningiomas not restricted to the cranial base who were treated with SRS reported an overall complication rate of 7.7% and a median time to complications of 11 months post-SRS. This very large series suggests that the median length of follow-up in our series should be sufficient to observe at least the majority of adverse events attributable to SRS.

Clinical improvement, defined as partial or complete resolution of pretreatment symptoms, was observed in the vast majority of patients. By contrast, only 13 patients experienced any post fSRS adverse event. Compared to the reported rates of mortality and morbidity after conventional surgical resection of cranial base tumors, (9% and 44%-56%, respectively) the relatively mild nature and low incidence of adverse events after fSRS appears to be acceptable for this very difficult to access anatomical region. Considering the relatively short progression free survival of the patients who underwent repeat resection of malignant disease, palliation of symptoms may be the principal objective. Among the 5 patients in this subset who had symptoms attributable to their disease at presentation, 4 of them experienced considerable improvement. Additional patients and quality of life measurement throughout follow-up would be valuable to better assess the utility of EES plus fSRS in this particular population.

In this heterogeneous group of patients with benign and malignant cranial base tumors, EESA followed by single or multisession fSRS produced a satisfactory local tumor control with an acceptable rate of post-operative and post-fSRS complications. Our series suggests that the use of EESA combined with an open approach may lead to increased post-operative complications compared to EESA alone. This reflects that these tumors were larger and more complex, requiring multiple surgical corridors to access these tumors effectively. Additional patients, institutions, and follow-up are needed to confirm these preliminary results.

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Received: May 18, 2010; Revised: July 26, 2010;
Accepted: August 2, 2010