Results of Anterior Skull Base Surgery in Pediatric and Young Adult Patients

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ABSTRACT

We sought to better define the results of anterior skull base surgery in pediatric and young adult patients. We performed a single-institution, retrospective cohort study in a tertiary-care academic cancer center. Between 1973 and 2005, 234 patients underwent anterior skull base surgery at Memorial Sloan-Kettering Cancer Center. Of these, 19 patients were <21 years of age. Surgical indications, findings, and complications were reviewed. Survival outcomes were analyzed using the Kaplan-Meier method and compared with patients ≥ 21 years old. Nineteen patients <21 years old underwent a total of 20 procedures for lesions of the anterior skull base. Sarcoma was the most common indication for surgery including 6 (32%) patients treated for radiation-induced malignancies. Minor complications were noted with 6 (30%) procedures. There were no major complications and no perioperative deaths. The difference in 3-year recurrence-free (68% versus 59%; $p=0.623$) and overall survival (83% versus 66%; $p=0.309$) compared with patients ≥ 21 years old did not reach statistical significance. Anterior skull base surgery is well tolerated in pediatric and young adult patients <21 years of age. Survival is comparable to older patients treated similarly and appears strongly influenced by histology.

KEYWORDS: Craniofacial resection, skull base surgery, pediatric, complications, survival

Malignancies of the anterior skull base are uncommon.¹ Of these, very few are observed among young patients. Not surprisingly, anterior skull base surgery is rarely indicated in pediatric and young adult patients, and outcomes of surgery for this patient population are poorly described. Results are often reported anecdotally or extrapolated from studies of older patients.²⁻⁴ Yet, there is little evidence to suggest that the biological behaviors of malignancies of the anterior skull base are similar between young and old patients. Pediatric and young adult patients lack the typical risk factors for sinonasal malignancies.⁵ Young patients are also less

likely to have significant comorbidities. So there remains a paucity of data to guide clinical decision making in young patients, particularly with respect to surgical management. The purpose of this study was to better define the results of anterior skull base surgery in patients <21 years of age.

MATERIALS AND METHODS

Inclusion criteria for this study included: (1) patient age <21 years old; (2) anterior skull base surgery including, but not limited, to craniofacial resection; and (3) medical

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records available for follow-up. The age limit used for this study is based on the definition established by the United States Food and Drug Administration for pediatric patients. Nineteen (8%) patients <21 years of age were identified from a prospective database of 234 patients who had anterior skull base surgery at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1973 and 2005. Demographic, clinical (prior treatments, extent of tumor invasion), surgical (approach, reconstruction), and pathological (histology, resection margins) characteristics were extracted from the medical record. Postoperative mortality, complications, length of hospital stay, and adjuvant treatments were also recorded. Complications were categorized into wound (infection, hematoma, flap failure), central nervous system (CNS; subdural hematoma, cerebrospinal fluid leak, meningitis, pneumocephalus), systemic, and orbital. Data collection for this study was approved by the MSKCC Institutional Review Board.

Patients were followed until the time of locoregional recurrence or death. Patients who did not develop locoregional recurrence by the time of last follow-up or death were censored. Results for patients <21 years of age were compared with 214 patients ≥21 years of age treated during the study period. The Wilcoxon rank sum test was used for comparison of continuous variables (age, length of hospital stay, and follow-up) between groups. Fisher exact two-tailed value and Pearson chi-square value tests were used for all other comparisons. Recurrence-free survival, disease-specific survival, and

overall survival were determined by the Kaplan-Meier method, and groups were compared by the log-rank test. A p value <0.05 was considered statistically significant. Statistical analyses were performed using JMP (version 4.0, SAS Institute Inc, Cary, NC) and SPSS (version 15.0, SPSS, Inc, Chicago, IL).

RESULTS

Patient characteristics are shown in Table 1. In patients <21 years of age, 16 (84%) were male, 3 (16%) were female, and the median age was 13 years (range 4 to 20). There was no significant difference in gender distribution between patients <21 and those ≥21 years of age. Only 1 (5%) of the patients <21 had a medical comorbidity (syndrome of inappropriate antidiuretic hormone) compared with 59 (28%) of the patients ≥21 years of age ($p=0.031$). However, 7 (37%) had a history of retinoblastoma, for which six of them had a history of prior radiation treatments. The proportion of patients with a history of radiation was similar between patients <21 (32%) and those ≥21 (24%, $p=0.584$) years of age. Yet, the proportion of patients <21 years of age with sarcoma histology was significantly greater than those ≥21 years of age (53% versus 14%, $p<0.0001$). Of the 10 patients with sarcoma, there were five osteosarcomas, three malignant fibrous histiocytomas, one fibrosarcoma, and one spindle cell sarcoma. Neoadjuvant therapy is commonly administered for pediatric patients with sarcoma. Therefore, it is not surprising that a greater percentage of

Table 1 Patient Characteristics

Variable	Age <21 y (n = 19)	Age ≥21 y (n = 214)	p Value
Gender, n (%)			
Male	16 (84.2)	142 (66.4)	0.130
Female	3 (15.8)	72 (33.6)	
Medical comorbidity, n (%)			
No	18 (94.7)	155 (72.4)	0.031
Yes	1 (5.3)	59 (27.6)	
Retinoblastoma, n (%)			
No	12 (63.2)	214 (100.0)	<0.0001
Yes	7 (36.8)	0 (0.0)	
Radiation exposure, n (%)			
No	13 (68.4)	156 (72.9)	0.584
Yes	6 (31.6)	52 (24.3)	
Not recorded	—	6 (2.8)	
Histology, n (%)			
Sarcoma	10 (52.6)	29 (13.5)	<0.0001
Other malignant	7 (36.9)	181 (84.6)	
Benign	2 (10.5)	4 (1.9)	
Neoadjuvant therapy, n (%)			
Yes	14 (73.7)	92 (43.0)	0.016
No	5 (26.3)	118 (55.1)	
Not recorded	—	4 (1.9)	

Table 2 Extent of Disease and Surgical Techniques

Variable	Age <21 y (n = 19*)	Age ≥21 y (n = 214)	p Value
Orbital Involvement, n (%)			
No	11 (55.0)	149 (69.6)	0.210
Yes	9 (45.0)	65 (30.4)	
Dural involvement, n (%)			
No	15 (75.0)	141 (66.2)	0.620
Yes	5 (25.0)	72 (33.8)	
Surgical approach, n (%)			
Anterior CF	16 (80.0)	174 (81.7)	0.633
Middle CF	2 (10.0)	11 (5.2)	
Anterior + middle CF	2 (10.0)	28 (13.2)	
Tracheostomy, n (%)			
No	17 (85.0)	192 (90.1)	0.443
Yes	3 (15.0)	21 (9.9)	
Reconstruction technique, n (%)			
GP	11 (55.0)	143 (66.8)	0.327
GP + free tissue transfer	9 (45.0)	71 (33.2)	
Margins, n (%)			
Positive	10 (50.0)	92 (43.6)	0.641
Negative	10 (50.0)	119 (56.4)	

*Nineteen patients, total 20 procedures.
CF, cranial fossa; GP, galeal-pericranial.

patients <21 (74%) years of age had received prior therapy than patients ≥21 (43%) years of age ($p=0.016$). Two (11%) of the patients <21 years of age had anterior skull base surgery for benign disease (plexiform neurofibroma, ossifying fibroma). The remaining malignancies included esthesioneuroblastoma,⁴ adenocarcinoma,¹ adenoid cystic carcinoma,¹ and neuroblastoma.¹

Details of the initial extent of disease and surgical techniques are shown in Table 2. One patient <21 years of age developed recurrent disease 2 years after initial craniofacial resection and was treated with a second surgery of the anterior skull base. Therefore, the data presented were based on a total of 20 procedures performed on 19 patients. Overall, there were no significant differences with respect to extent of disease and surgical techniques between patients <21 years of age and those ≥21 years of age. In patients <21 years of age, there was orbital involvement in 9 (45%) cases and dural involvement in 5 (25%). The majority (80%) of procedures involved only the anterior cranial fossa, and tracheostomy was rarely required (15%). Surgical margins were similar between groups. Margins were close or microscopically positive in 10 (50%) patients <21 compared with 92 (44%) patients ≥21 years of age ($p=0.641$). All patients <21 were reconstructed using a galeal-pericranial flap. In addition, 9 (45%) required free tissue transfer reconstruction: rectus abdominus in six, latissimus dorsi in two, and radial forearm in one.

Details of complications, adjuvant therapy, and follow-up are shown in Table 3. Overall, complications

were not significantly different between patient groups. There were no postoperative deaths among patients <21 years of age and 9 (4%) deaths among patients ≥21 years of age. This difference was not statistically significant. Six (30%) patients <21 experienced a complication compared with 92 (43%) patients ≥21 years of age ($p=0.345$). Complications consisted of two wound complications (cellulitis, minor dehiscence), two hematomas, and two minor orbital complications (nasolacrimal duct obstruction, diplopia). No CNS or systemic complications were observed among patients <21 years of age. The CNS complication rate was significantly greater in patients ≥21 years of age ($p=0.016$). The median hospital stay was 13 days (range, 7 to 26) for patients <21 years of age. Seventy percent of patients <21 received adjuvant radiation therapy compared with 44% of patients ≥21 years of age ($p=0.069$). Conversely, fewer patients <21 received adjuvant chemotherapy (40% versus 89%, $p<0.0001$). The median follow-up for patients <21 years of age was 34.2 months (range, 0.7 to 186.3).

Excluding those with benign disease, 9 of 17 (53%) patients <21 years of age developed recurrence including: local in four, distant in three, and a combination of local and distant recurrence in two. At 3 years, recurrence-free survival was 68% for patients <21 years and 59% for patients ≥21 years of age ($p=0.623$; Fig. 1). Three-year disease-specific and overall survivals were nearly overlapping. At 3 years, overall survival was 83% for patients <21 years and 66% for patients ≥21 years of age ($p=0.309$; Fig. 2). When stratified by histology

Table 3 Complications, Adjuvant Therapy, and Follow-up

	Age <21 y (n = 20*)	Age ≥21 y (n = 214)	p Value
Complications, n (%)			
Overall	6 (30.0)	92 (43.0)	0.345
Mortality	—	9 (4.2)	NS
Wound	4 (20.0)	52 (24.3)	0.790
Infection, minor	2 (10.0)	14 (6.5)	
Infection, major	—	16 (7.5)	
Hematoma	2 (10.0)	15 (7.0)	
Flap (FTT) loss	—	1 (0.5)	
Other	—	6 (2.8)	
Central nervous system	—	14 (6.5)	0.016
Subdural hematoma	—	10 (4.7)	
CSF leak	—	11 (5.1)	
Meningitis	—	10 (4.7)	
Pneumocephalus	—	10 (4.7)	
Other	—	5 (2.3)	
Systemic	2 (10.0)	19 (8.9)	0.383
Orbital	—	7 (3.2)	0.174
Hospital stay (d)			
Median (range)	13 (7–26)	14 (2–91)	0.160
Adjuvant radiation, n (%) [†]			
No	14 (70.0)	95 (44.4)	0.069
Yes	6 (30.0)	103 (48.1)	
Not recorded	—	16 (7.5)	
Adjuvant chemotherapy, n (%) [†]			
No	8 (40.0)	9 (89.3)	<0.0001
Yes	12 (60.0)	4 (6.5)	
Not recorded	—	2 (4.2)	
Follow-up, mo*			
Median (range)	34.3 (0.7–186.3)	26.5 (0.1–236.8)	0.580

*Nineteen patients; total 20 procedures.

[†]Includes two patients with benign disease.

FTT, free tissue transfer; CSF, cerebral spinal fluid; NS, not significant.

(sarcoma versus other), there appeared to be a difference in 3-year overall survival (75% versus 100%) but this did not reach statistical significance ($p = 0.256$; Fig. 3).

DISCUSSION

There are very few reports describing the results of skull base surgery in pediatric and young adult patients. In 1999, Teo et al reported a series of 26 pediatric patients who underwent a variety of skull base approaches for the resection of benign and malignant skull base tumors.⁶ Five of these patients were treated via anterior craniofacial resection for either esthesioneuroblastoma,² fibrous dysplasia,² or ossifying fibroma.¹ There were no reported complications, and 80% (4/5) of patients were alive after an average follow-up of nearly 2 years. In 2003, Brockmeyer et al reported their experience with 55 pediatric patients undergoing skull base surgery.⁷ Most patients in this series had benign disease, and only seven had pathology involving the

nasomaxillary region. There were no infections, cerebral spinal fluid leaks, or deaths reported. In 2006, Howard et al reported a 25-year experience of craniofacial resection for tumors of the nasal cavity and paranasal sinuses.² The data presented appeared to include ~5 patients <10 years of age and ~28 patients 11 to 20 years of age. However, there was no analysis of outcomes of pediatric and young adult patients described. The International Collaborative Study of Craniofacial Surgery for Malignant Skull Base Tumors reported the largest number of pediatric and young adult patients including the patients presented in our study.⁸ In that study, 81 of 1307 (6.2%) patients were <20 years of age. There was a trend toward improved overall survival for patients ≤50 (57%) compared with those >50 (51%, $p = 0.08$) years of age. Results were not reported specifically for patients <20 years of age. Most recently, the data from that study were reanalyzed for patients <21 years of age.⁹ With a median follow-up of 30 months, the authors reported a 5-year overall

Figure 1 Three-year recurrence-free survival of patients <21 years undergoing anterior skull base surgery compared with patients ≥21 years of age.

survival of 55%. Those results are similar to the overall survival for the entire international cohort (54%), suggesting that the survival of pediatric patients is comparable to that of adults.

In this study, we report the outcome of 19 pediatric and young adult patients undergoing anterior skull base surgery at a single institution. We found significant differences between the baseline characteristics of

Figure 2 Three-year overall survival of patients <21 years undergoing anterior skull base surgery compared with patients ≥21 years of age.

Figure 3 Three-year overall survival of patients <21 years of age undergoing anterior skull base surgery stratified by histology.

patients <21 and those ≥ 21 years of age. Younger patients were less likely to have a comorbidity. More importantly, the younger cohort had a significantly greater percentage of patients with sarcoma histology. Seven patients <21 years of age had a history of retinoblastoma, and six had a history of radiation, a known risk factors for sarcoma.¹⁰ Pediatric malignancies, sarcomas in particular, are often treated with neoadjuvant chemotherapy. So it is not surprising that 74% of the patients included in this cohort received neoadjuvant therapy. There were no significant difference in extent of disease and surgical technique between patients <21 and those ≥ 21 years of age.

Consistent with prior reports, there were few complications noted among patients <21 years of age.^{6,7,9} When complications were encountered, they were generally less severe than those reported in older patients. For example, there were no deaths and no CNS complications noted among patients <21 compared with 9 (4.2%) deaths and 14 (6.5%) CNS complications for patients ≥ 21 years of age. The difference in CNS complications was significant. The most common complications were minor wound infections and hematomas. Despite fewer complications for younger patients, the median hospital stay was not significantly different than the hospital stay for the older cohort. Reasons for extended hospitalization were not elucidated in this study. It is possible that the nonmedical factors influenced the length of hospitalization disproportionately, as well as the frequent use of free tissue

transfer, which tends to increase postoperative hospitalization.

In this study, there was a trend toward improved survival for patients <21 years of age. We excluded cases of benign histology for survival analyses. We hypothesized that survival would be improved for patients <21 years of age given fewer comorbidities and a more favorable predicted pathologic profile (e.g., fewer squamous cell carcinoma, sinonasal mucosal melanoma, etc.). At 3 years, recurrence-free survival was 68% for patients <21 and 59% for patients ≥ 21 years of age. Overall survival was 83% for patients <21 and 66% for patients ≥ 21 years of age. However, these differences did not reach statistical significance, possibly due to the small sample size. Our results are better than those previously reported (83% 5-year overall survival versus 55%).⁹ The results are most striking when stratified by histology. At 3 years, we found that the overall survival of patients <21 years of age with sarcoma histology was 75% compared with 100% for those with other malignancies. Longer follow-up is needed to determine whether or not this difference is sustained.

Prospective multi-institutional data will be required to determine whether or not patients <21 have better outcomes than patients ≥ 21 years of age. The number of pediatric and young adult patients requiring anterior skull base surgery is very small, and margin status has been shown to be an important prognostic factor for patients undergoing craniofacial resection for sinonasal malignancies.¹¹ Therefore, in young

patients an aggressive approach may be most warranted. In this study, all patients treated for malignancy received neoadjuvant and/or adjuvant therapy. Clearly these patients are best treated at tertiary care cancer centers where multidisciplinary care can be well coordinated.

None of the patients included in this study were treated via an endoscopic or endoscopic-assisted approach. Many were treated before endoscopic resection was feasible. Given current technology, it is unknown how many patients could have had an endoscopic resection. Regardless of technique, there are unique factors to be considered when contemplating anterior skull base surgery in young patients. The small size and thin bone of the calvarium requires special care.⁷ The frontal sinuses may be absent or poorly pneumatized in pediatric patients.¹² Likewise, traditional landmarks of the anterior skull base such as the supraorbital notch may be blunted or absent in young patients. Finally, skull base surgery can impact facial and cranial bone growth. Therefore, these patients should be evaluated and treated on an individual basis by an experienced team of surgeons.

CONCLUSIONS

Anterior skull base surgery is well tolerated in patients <21 years of age. The survival of pediatric and young adult patients is comparable to that of older patients treated similarly. Prospective multi-institutional data are needed to more accurately define the impact of young age on outcome after anterior skull base surgery for malignancy.

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