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Skull Base Surgery in the Pediatric Population—The 2nd International Collaborative Study (1995–2015)

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ABSTRACT

Background: The current study presents the efforts of a global collaborative group to review the management and outcomes of malignant tumors of the skull base in the pediatric population worldwide.

Patients and Methods: A total of 28 institutions contributed data on 3061 patients. From this, there were 64 pediatric patients (2.1%). Clinical variables, overall and disease-free survival (OS and DFS) outcomes, and multivariable factors associated with outcome were evaluated.

Results: The male-to-female ratio was 37:27 and the median [IQR] age at diagnosis was 14.0 [9.6–16.0] years. The most common malignancy was sarcoma (57.8%), followed by esthesioneuroblastoma (25.0%) and carcinoma (17.2%). Negative margins were achieved in 53.1% children. Dural invasion was associated with reduced OS and DFS. Adjuvant radiotherapy was associated with improved survival outcomes.

Conclusions: Open approaches were widely used for pediatric skull base tumor resection in the period between 1995 and 2015 but we saw a rise in the use of endoscopic and combined techniques by the end of the period covered by this study. Our results may represent a transitional era in which alternative endoscopic techniques continue to expand.

1 | Introduction

Surgery of skull base tumors has changed dramatically over the past four decades due to advancements with the collaboration of various medical and surgical disciplines. These advancements have improved the long-term survival rates and the quality of life of patients undergoing skull base and craniofacial resections for tumor excision. Various approaches have been used over the years with the aim of devising the best surgical approaches to achieve these goals in adults [1–4]. However, the rarity of malignant skull base lesions in the pediatric population has restricted the advancement of our determining the best surgical approach for children and adolescents. There are several fundamentally unique characteristics of the pediatric population that differentiate it from that of adults, making it impossible to apply evidence from adults to them. First, anatomical considerations differ due to unique proportions of cranial fossa dimensions, paranasal sinus developments, eruption status of permanent teeth, and the absolute available volume for reconstruction [5–8]. Second, the rarity and heterogeneity of these pathologies do not allow for strong

For affiliations, refer to page 12.

Dan M. Fliss and Omer J. Ungar are contributed equally to this work.

TABLE 1 | Patient demographics and surgical approach.

	Open ($n=38$)	Endoscopic ($n=8$)	Combined ($n=18$)	Total ($n=64$)
Males; *n* (%)	20	5	12	37
Females; *n* (%)	18	3	6	27
Age < 8 years	9	1	2	12
Age ≥ 8 years	29	7	16	52

evidence-based data in large numbers [9]. Third, bony growth centers in the cranial and facial skeleton might be violated by osteotomies, negatively impacting the physiological development of the face and paranasal sinuses and resulting in compromised aesthetic and functional outcomes [6, 7, 10].

Given the rarity of skull base pathologies in the pediatric population, the acquisition of meaningful results required the collaboration of multiple medical centers. Such collaborations have been conducted with data from 28 institutions, involving 3061 skull base resections performed between 1995 and 2015, with 64 (2.1%) of these procedures carried out on pediatric patients [4]. This paper provides descriptions of the clinical presentations, various pathologies, surgical approaches, complications, therapeutic options, and outcomes of skull base surgeries conducted on children and adolescents.

2 | Materials and Methods

2.1 | Ethical Considerations

Local institutional review board (IRB) approval for this analysis was obtained from each participating institution. Informed consent to use the anonymized data was waived.

2.2 | Patient Selection

Details of the medical center enrollment were described in an earlier report on the combined worldwide case series [4]. In brief, included were pediatric patients (age < 18 years old at surgery) who underwent skull base resection or craniofacial surgery for malignant tumor resection in 28 centers between 1995 and 2015. Sixty-four patients were eligible for the current study.

2.3 | Data Entry, Audit, and Analysis

A data transfer agreement was signed by each of the enrolled medical centers. Each participant had a secured link to a standard database template by means of a Research Electronic Data Capture tool. Data analysis was performed in a centralized manner in the Department of Biostatistics at Memorial Sloan Kettering Cancer Center (NY, USA).

2.4 | Statistical Methods

Categorical variables were summarized as frequencies and percentages. Age was evaluated for normal distribution by the use of histograms and the Kolmogorov–Smirnov test and reported as medians and interquartile ranges [IQR]. The cohort was divided categorically by age < 8 versus age ≥ 8 for analysis. The 8-year cutoff was chosen in order to be consistent with the International Collaborative Study publication [11]. A Kaplan–Meier curve was used to assess overall (OS) and disease-free survival (DFS) throughout the follow-up period. Univariate cox regression was used to evaluate the hazard ratio and 95% confidence interval (CI) for each predictor of the studied outcome. The log rank test was used to determine the association between categorical parameters and the studied outcome. The association between categorical variables was evaluated by using Fisher's Exact test. The association between age and other categorical variables was evaluated by the Mann–Whitney test. The Kruskal-Wallis test was used for evaluating the association between age and categorical variables composed of more than 2 categories. The Dunn test was applied for post hoc analysis. All statistical analysis was performed using NCSS 2024 Statistical Software (2024). NCSS LLC. Kaysville, Utah, USA.

3 | Results

3.1 | Demographics

A total of 28 centers from 5 continents participated in this international collaborative study. The 64 cases that fulfilled study inclusion criteria had a male-to-female ratio of 37:27 (57.8%–42.2%) (Table 1). The cohort's age at diagnosis was not distributed normally, with a median [IQR] age of 14.0 [9.6–16.0] years (Figure 1). The median age at diagnosis was not significantly different between males and females (14.4 years and 13.3 years, respectively, $p=0.407$).

3.2 | Pathologies, Tumor Anatomy, Surgical Approaches, Reconstructions and Complications

The most common malignancy was sarcoma (37, 57.8%), the majority of which were soft tissue sarcomas (20, 31.3%). The next most common malignancy was esthesioneuroblastoma (16, 25.0%), of which 13 were classical esthesioneuroblastomas, and three were other variants, which were classified as such due to other histologic features.

The least common malignancy was carcinoma (11, 17.2%), of which 9 were adenoid cystic carcinomas. There was no association between sex and age of diagnosis ($p=0.407$). Neither age nor sex was associated with pathology ($p=0.238$ and $p=0.609$, respectively). Table 2 lists the types of malignancies and their

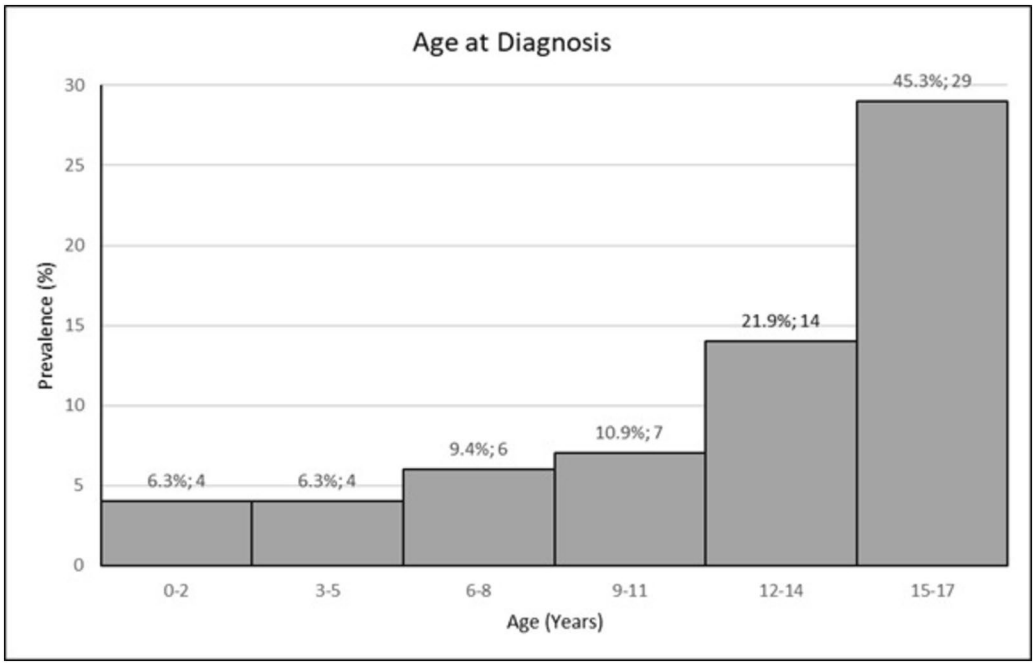

FIGURE 1 | Age at diagnosis.

prevalences. Figure 2A represents the age groups and the histology at presentation. Most (81.3%) of the tumors were diagnosed in the 8–18 years age group.

The most common tumor epicenter was the paranasal (mostly maxillary) sinus (31, 48.4%), followed by the nasal cavity (16, 25.0%). When combined, the sinonasal airway system comprised 47 (73.4%) of the cases followed by the pterygopalatine fossa (PPF) with 5 (7.8%) cases. All of the other epicenters had a maximal prevalence of 2 (3.1% per epicenter) (Table 3).

Tumor extension to the orbit, infratemporal fossa (ITF), PPF, skin, and skull base was also documented, with all 64 of the tumors extending to the anterior or middle fossa skull base (48, 75.0% and 16, 25.0%, respectively). The most common skull base invasion extended to the bony skull base (45, 70.3%) and dura (12, 18.8%), while direct brain parenchymal invasion was reported in 7 (10.9%) cases (all to the anterior skull base). The next most invaded site was the orbit (32 cases, 50.0%). Orbital invasion extended to the bony orbital wall in 5 (7.8%) cases and to the orbital periosteum in 12 (18.8%) cases. Direct orbital content invasion was reported in 15 (23.4%) cases. ITF, PPF, and skin invasions were documented in 24 (37.5%), 16 (25.0%), and 9 (14.1%) cases, respectively (Table 3).

Cranial nerve (CN) deficit was documented in 14 (21.9%) cases upon presentation. The most common CN deficits were the optic (CN II) and oculomotor (CN III) nerves (6 cases, 9.4% and 5 cases, 7.8%, respectively). Other CN deficits were recorded in CNs IV, V, VI, VII, and XII (2–3 cases each). The relatively high number of CN II and CN III deficits is in line with the high intraorbital content invasion described previously.

The surgical approach was individually tailored by tumor extension, availability of endoscopic service in a given medical center, and surgical expertise of the health providers team.

TABLE 2 | Tumor distribution by histology.

Tumor; *n* (%)		***n* (%)**
Sarcoma 37 (57.8)	Osteosarcoma	10 (15.6)
	Primitive neuroectodermal tumor	7 (10.9)
	Rhabdomyosarcoma	4 (6.3)
	Chondrosarcoma	4 (6.3)
	Liposarcoma	3 (4.7)
	Pleomorphic spindle cell sarcoma	3 (4.7)
	MPNST	2 (3.1)
	Synovial sarcoma	2 (3.1)
	Teratocarcinosarcoma	2 (3.1)
Esthesioneuroblastoma 16 (25.0)	Classical esthesioneuroblastoma	13 (20.3)
	Esthesioneuroblastoma variants	3 (4.7)
Carcinoma 11 (17.2)	Adenoid cystic carcinoma	9 (14.1)
	Mucoepidermoid carcinoma	1 (1.6)
	Adenocarcinoma	1 (1.6)
Total; *n* (%)		64 (100)

Abbreviation: MPNST, malignant peripheral nerve sheath tumor.

Open resections were performed in 38 (59.4%) cases, pure endoscopic resections in 8 (12.5%) cases, and a combination of the 2 in 18 (28.1%) cases (Table 3). A temporal analysis was

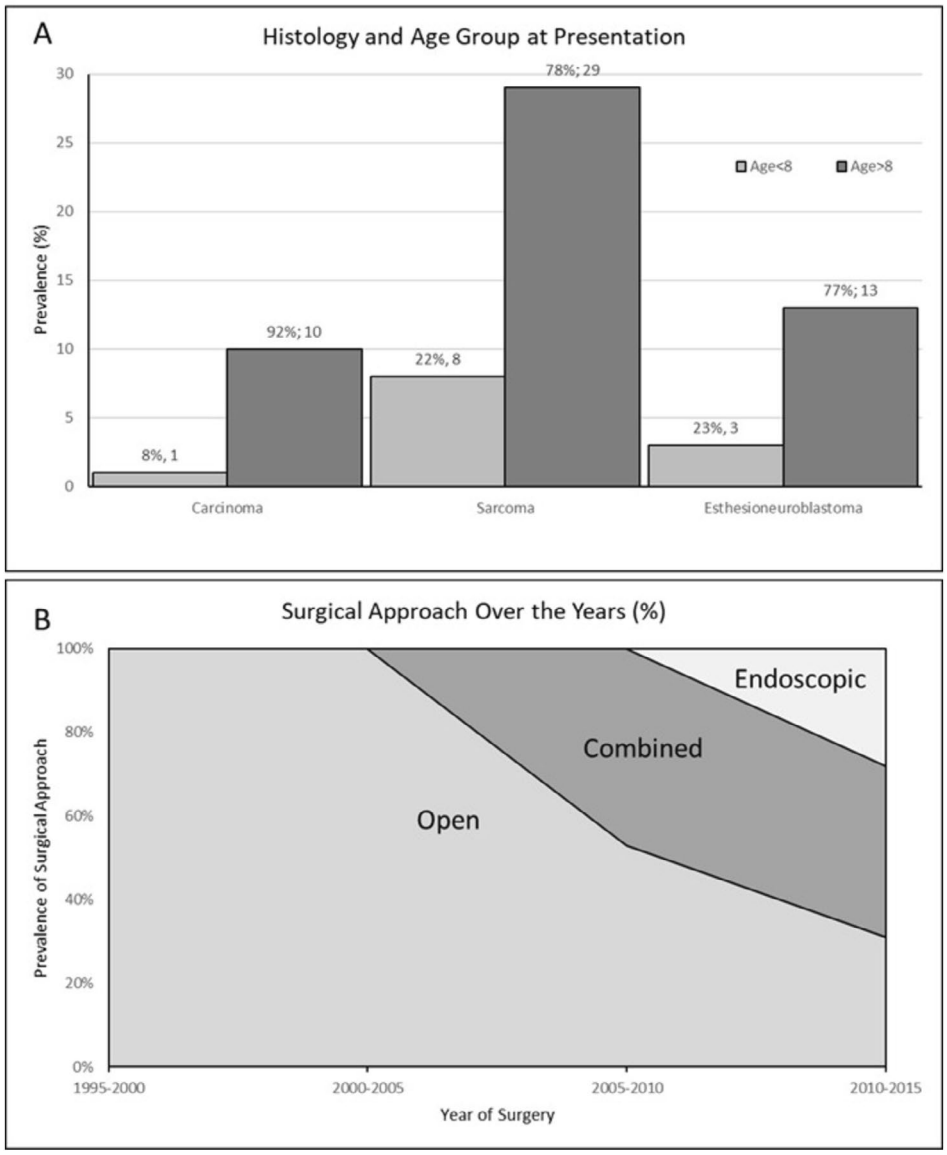

FIGURE 2 | (A) Histology and age group at presentation. (B) Surgical approach as a function of operation year.

performed to study the distribution of the surgical approach during the year of surgery. Between 1995 and 2005, 20 surgeries were performed, all of which were carried out via the open approach. During 2005–2010, 15 surgeries were performed, and they were distributed almost evenly between the pure open approach and the combined (open and endoscopic) approaches (8 and 7 surgeries, respectively). During the 2010–2015 years, 29 surgeries were performed with a 9:12:8 ratio for the pure open, combined and pure endoscopic approaches, respectively (Figure 2B).

Free flaps comprised the most commonly used reconstruction modality (32, 50.0%), with galeal pericranial and nasoseptal flaps having been used in 11 (17.2%) cases each. Other grafts (fascia lata and skin grafts) were used in 7 (10.9%) and 3 (4.7%) cases, respectively. Alloplastic material was used in 3 (4.7%) cases. There was a dependency of the reconstruction material as a function of the surgical approach. Specifically, free flaps were used only following open resections (solely open or combined approach), while no nasoseptal flaps were used following open resections. Skin grafting was used only following open resections since skin invasion is a relative contraindication for endoscopic resection (Table 3).

The overall complication rate for all 64 surgeries was 50.0% (32 cases). The most common complication was wound dehiscence (10 cases, 15.6%). There were 4 (6.3%) cases of flap necrosis and 3 (4.7%) cases of surgical site infection. Most of these complications occurred in previously operated and/or irradiated sites, which were too small to reach a level of significance. Six (9.4%) patients underwent a revision within 7 days postoperatively. Bacteremia and deep vein thrombosis were reported in 4 (6.3%) and 2 (3.1%) cases, respectively. There were no surgery-related deaths. The risk of complications as a function of surgical approach could not be calculated due to low power. Postoperative complications are shown in Table 3.

TABLE 3 | Tumor distribution reconstruction, complications and surgical approach.

	Open ($n=38$)	Endoscopic ($n=8$)	Combined ($n=18$)	Total ($n=64$)
Tumor epicenter				
Infratemporal fossa; *n* (%)	1 (1.6)			1 (1.6)
Pterygopalatine fossa; *n* (%)	2 (3.1)		3 (4.7)	5 (7.8)
Paranasal Sinuses; *n* (%)	16 (25.0)	3 (4.7)	12 (18.8)	31 (48.4)
Nasal cavity; *n* (%)	11 (17.2)	2 (3.1)	3 (4.7)	16 (25.0)
Nasopharynx; *n* (%)		2 (3.1)		2 (3.1)
Anterior skull base; *n* (%)	2 (3.1)			2 (3.1)
Middle skull base; *n* (%)		1 (1.6)		1 (1.6)
Parotis; *n* (%)	2 (3.1)			2 (3.1)
Orbit; *n* (%)	2 (3.1)			2 (3.1)
Temporal bone; *n* (%)	1 (1.6)			1 (1.6)
Mandible; *n* (%)	1 (1.6)			1 (1.6)
Tumor extension[a]				
Orbit; *n* (%)	30 (46.9)		2 (3.1)	32 (50.0)
Skin; *n* (%)	8 (12.5)		1 (1.6)	9 (14.1)
Pterygopalatine fossa; *n* (%)	8 (12.5)	3 (4.7)	5 (7.8)	16 (25.0)
Infratemporal fossa; *n* (%)	14 (21.9)	3 (4.7)	7 (10.9)	24 (37.5)
Skull base; *n* (%)	38 (59.4)	8 (12.5)	18 (28.1)	64 (100)
Reconstruction[b]				
Free flap; *n* (%)	31 (48.4)		1 (1.6)	32 (50.0)
Galeal pericranial flap; *n* (%)	5 (7.8)		6 (9.4)	11 (17.2)
Nasoseptal flap; *n* (%)		6 (9.4)	5 (7.8)	11 (17.2)
Fascia lata graft; *n* (%)	2 (3.1)	2 (3.1)	3 (4.7)	7 (10.9)
Skin graft; *n* (%)	1 (1.6)		2 (3.1)	3 (4.7)
Alloplastic material; *n* (%)	1 (1.6)		2 (3.1)	3 (4.7)
Complications[c]				
Surgical site infection; *n* (%)	2 (3.1)		1 (1.6)	3 (4.7)
Wound dehiscence; *n* (%)	6 (9.4)		4 (6.3)	10 (15.6)
Diplopia; *n* (%)	1 (1.6)	2 (3.1)		3 (4.7)
Flap necrosis; *n* (%)	3 (4.7)		1 (1.6)	4 (6.3)
Bacteremia; *n* (%)	2 (3.1)	1 (1.6)	1 (1.6)	4 (6.3)
Deep vein thrombosis; *n* (%)	1 (1.6)		1 (1.6)	2 (3.1)
Revision within 7 days; *n* (%)	5 (7.8)		1 (1.6)	6 (9.4)
Death; *n* (%)	0 (0)	0 (0)	0 (0)	0 (0)
Any complication; *n* (%)	20 (31.3)	3 (4.7)	9 (14.1)	32 (50.0)

[a]A single tumor can extend to more than one site.
[b]A single surgical defect can be reconstructed by more than 1 reconstruction modality.
[c]A single surgery can include more than 1 complication.

3.3 | Margins Analyses and Perineural Invasion

Thirty-four (53.1%) of the specimens' margins were free of tumor. Close margins (defined as a minimal distance between tumor and margin of <2 mm) were found in 11 (17.2%) specimens, and positive margins were reported in 19 (29.7%) specimens. Perineural invasion was reported in 14 (21.9%) specimens. As expected, the majority of perineural invasions were diagnosed

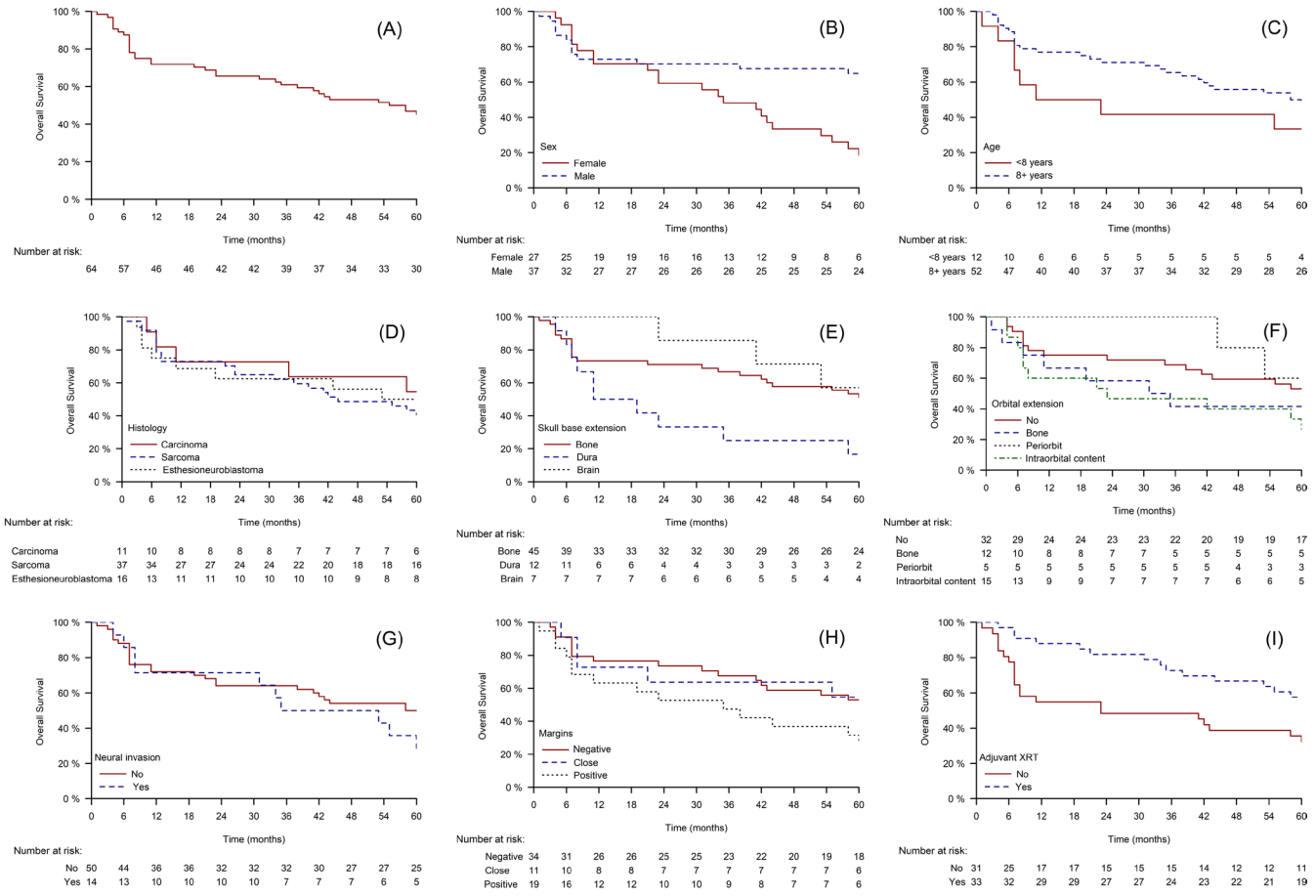

FIGURE 3 | Kaplan–Meier curves for overall survival. (A) Overall survival for the entire cohort; (B) Sex; (C) Age; (D) Pathology; (E) Skull base invasion; (F) Orbital invasion; (G) Neural invasion; (H) Margins; (I) Adjuvant radiotherapy. [Color figure can be viewed at wileyonlinelibrary.com]

in patients with adenoid cystic carcinoma of the sinonasal cavity based upon their neurotropic characteristics. Most patients with histologically confirmed perineural invasion presented with major CN deficit.

3.4 | 5 Year Overall Survival

The 5 year OS rate (Figure 3) was identical to the disease-specific survival rate (46.9%). Age at diagnosis was not associated with any influence on OS ($p = 0.470$). In contrast, sex correlated significantly with OS: male sex was associated with better OS (survival probability = 0.625, 95% confidence interval [CI] 0.475–0.775) compared to female sex (survival probability = 0.185, 95% CI 0.039–0.332), $p = 0.002$. Previous surgery and previous adjuvant therapy were not significantly associated with OS ($p = 0.680$ and $p = 0.276$, respectively). Adjuvant radiotherapy in association with the index surgery, however, was associated with better OS: survival probability = 0.571, 95% CI 0.408–0.735 with adjuvant radiotherapy versus survival probability = 0.313, 95% CI 0.152–0.473 without adjuvant radiotherapy, $p = 0.011$. Orbital extension did not correlate with OS, regardless of extension depth (bone, dura, or intraorbital content, $p = 0.272$). In contrast, skull base extension was found to compromise OS when invasion was as deep as the skull base dura compared to bone (i.e., sparing of the dura), with a survival probability of 0.500, 95% CI 0.359–0.641 for bone compared to 0.167, 95% CI < 0.001–0.378 for dura ($p = 0.032$). The differential histologic diagnosis (sarcoma, esthesioneuroblastoma, versus carcinoma) was not associated with OS ($p = 0.895$). Interestingly, margin status and perineural invasion were not significantly correlated with OS ($p = 0.261$ and $p = 0.261$, respectively). The occurrence of any complication also did not compromise OS ($p = 0.902$) (Table 4). Hazard ratios (HR) for OS are given in Table 5, and Kaplan–Meier OS survival curves are shown in Figure 3.

3.5 | 5 Year Disease-Free Survival

The overall DFS was 34.4% and it correlated significantly with sex and the provision of adjuvant radiotherapy (Figure 4). Male sex was associated with a favorable DFS (survival probability = 0.525, 95% CI 0.370–0.680) compared to female sex (survival probability = 0.074, 95% CI < 0.001–0.173, $p < 0.001$). Previous surgery and previous adjuvant chemotherapy were not associated with a favorable DFS ($p = 0.559$ and $p = 0.710$, respectively). Adjuvant radiotherapy had a longer DFS interval during the follow-up period (survival probability = 0.486, 95% CI 0.320–0.651 with radiotherapy, compared to survival probability = 0.188, 95% CI = 0.052–0.323 without radiotherapy, $p = 0.001$). Tumor extensions to the orbit or to the skull base, as well as histological diagnosis, margin status, perineural invasion, or any

TABLE 4 | Overall and disease-free survival.

Variables		OS			DFS		
		Survival	95% CI	*p*-value	Survival	95% CI	*p*-value
Age	< 8	0.333	0.067–0.0600	0.202	0.250	0.005–0.495	0.224
	≥ 8	0.473	0.341–0.605		0.364	0.237–0.491	
Sex	Male	0.625	0.475–0.775	**0.002**	0.525	0.370–0.680	**< 0.001**
	Female	0.185	0.039–0.332		0.074	< 0.001–0.173	
Histology[a]	Carcinoma	0.545	0.251–0.840	0.895	0.364	0.079–0.648	0.510
	Sarcoma	0.405	0.247–0.564		0.270	0.127–0.413	
	Blastoma	0.500	0.255–0.745		0.500	0.255–0.745	
Orbital extension	No	0.529	0.361–0.697	0.272	0.412	0.246–0.577	0.324
	Bone	0.417	0.138–0.696		0.250	0.005–0.495	
	Periosteum	0.500	0.100–0.900		0.333	< 0.001–0.711	
	Intraorbital content	0.267	0.043–0.491		0.267	0.043–0.491	
SB extension	Bone	0.500	0.359–0.641	**0.032**	0.375	0.238–0.512	0.066
	Dura	0.167	< 0.001–0.378		0.167	< 0.001–0.378	
	Brain	0.571	0.205–0.938		0.429	0.062–0.795	
Margins	Negative (> 2 mm)	0.500	0.337–0.663	0.122	0.333	0.179–0.487	0.098
	Close (< 2 mm)	0.583	0.304–0.862		0.583	0.304–0.862	
	Positive	0.263	0.065–0.461		0.211	0.027–0.394	
Neural invasion	Yes	0.286	0.049–0.522	0.261	0.214	< 0.001–0.429	0.381
	No	0.491	0.356–0.625		0.374	0.247–0.508	
Previous surgery	Yes	0.471	0.233–0.708	0.680	0.412	0.178–0.646	0.559
	No	0.440	0.302–0.578		0.320	0.191–0.449	
Adj. chemo.	Yes	0.565	0.363–0.768	0.276	0.348	0.153–0.543	0.710
	No	0.386	0.243–0.530		0.341	0.201–0.481	
Adj. radiotherapy	Yes	0.571	0.408–0.735	**0.011**	0.486	0.320–0.651	**0.001**
	No	0.313	0.152–0.473		0.188	0.052–0.323	

Abbreviations: Adj., Adjuvant; Chemo, chemotherapy; CI, confidence interval; DFS, disease-free survival; OS, overall survival; SB, skull base.
[a]Benign pathologies were omitted.

complication did not correlate with DFS ($p = 0.324$, $p = 0.066$, $p = 0.510$, $p = 0.098$, $p = 0.381$, and $p = 0.194$, respectively). The data on OS are given in Table 4, and the HR for OS is given in Table 5. Kaplan–Meier OS survival curves are shown in Figure 4. Comparison between OS and DFS is shown in Figure 5.

4 | Discussion

Skull base tumors are rare among adults and even more so among the pediatric population. An earlier study described international collaboration in skull base surgery for malignant tumors in 84 pediatric and adolescent patients (84/1307 = 6.4%) treated between 1956 and 2000 in 17 medical centers around the world [11]. Our current study includes 64 patients treated from 1995 to 2015 at 28 academic institutions across five continents. Our updated results describe what could be considered a transitional era in which endoscopic techniques continue to expand as alternative approaches for these potentially lethal tumors of the skull base occurring in the pediatric population. We evaluated their impact on the outcomes of skull base tumor management in the last 20 years.

Significant recent advancements have revolutionized the capabilities of diagnosing and treating tumors of the skull base, including improved imaging technologies, neoadjuvant therapies, endoscopic instruments and techniques, intraoperative navigation, advanced intensive care units, standardized infection prevention protocols, and more precise radiotherapy and chemotherapy [3]. While these advancements were originally developed for the adult population, they can generally be applied to the pediatric population as well.

This collaborative effort faced several challenges, particularly due to the increasing regulatory demands imposed on

TABLE 5 | Hazards ratio of overall and disease-free survival.

		OS			DFS		
Variables		**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age[a]		0.977	0.916–1.041	0.47	0.981	0.925–1.042	0.536
Sex	Female	Ref (1)			Ref (1)		
	Male	0.368	0.119–0.716	**0.003**	0.349	0.188–0.649	**< 0.001**
Histology[b]	Carcinoma	Ref (1)			Ref (1)		
	Sarcoma	1.071	0.252–4.559	0.926	1.671	0.397–7.040	0.484
	Blastoma	0.914	0.194–4.310	0.910	0.966	0.205–4.551	0.965
Orbital extension	No	Ref (1)			Ref (1)		
	Bone	1.529	0.629–3.720	0.349	1.637	0.742–3.610	0.222
	Periosteum	0.862	0.251–2.961	0.813	0.881	0.301–2.581	0.818
	Intraorbital content	1.996	0.925–4.307	0.078	1.764	0.844–3.688	0.131
SB extension	Bone	Ref (1)			Ref (1)		
	Dura	2.450	1.159–5.181	0.019	2.264	1.093–4.866	**0.028**
	Brain	0.724	0.218–2.406	0.598	0.884	0.311–2.511	0.817
Margins	Negative (> 2 mm)	Ref (1)			Ref (1)		
	Close (< 2 mm)	0.808	0.200–2.177	0.673	0.560	0.213–1.470	0.239
	Positive	1.862	0.925–3.749	0.082	1.589	0.831–3.037	0.161
Neural invasion	Yes	Ref (1)			Ref (1)		
	No	1.494	0.722–3.091	0.279	1.349	0.681–2.673	0.392
Previous surgery	No	Ref (1)			Ref (1)		
	Yes	0.851	0.401–1.803	0.673	0.811	0.400–1.641	0.560
Adj. chemo.	No	Ref (1)			Ref (1)		
	Yes	0.672	0.325–1.390	0.284	1.125	0.603–2.098	0.712
Adj. radiotherapy	No	Ref (1)			Ref (1)		
	Yes	0.434	0.225–0.839	**0.013**	0.378	0.06–0.693	**0.002**

Note: The bold values are the significant values, *p*-value below 0.05 is considered statistically significant.
Abbreviations: Adj, adjuvant; Chemo, chemotherapy; CI, confidence interval; DFS, disease-free survival; Ext, extension; HR, hazard ratio; OS, overall survival; Ref, reference value (Hazard = 1); SB, skull base.
[a]Per year.
[b]Benign cases were omitted.

participating institutions. Unlike the earlier study, which relied on manual paper-based data collection, this project utilized a unified, secure web platform for streamlined data collection and analysis. However, implementing this platform required extensive communication and negotiations, including the involvement of legal teams from all 28 institutions. Despite the commitment and dedication of institutional leaders to advancing high-quality research in this domain, it took nearly 2 years to finalize legal agreements between each institution and the central data repository at Memorial Sloan Kettering Cancer Center before statistical analysis could begin. This achievement reflects the shared vision and determination of the collaborative team to push the boundaries of research in skull base surgery in general and pediatric skull base surgery in particular.

Pediatric skull base surgery for malignant tumors is constantly changing in association with advances in patient selection, postoperative management and adjuvant therapies. These modifications usually follow the adult skull base surgical features, although pediatric skull base surgery is also additionally associated with unique considerations. Intercarotid distance, sinus pneumatization, craniofacial growth centers and other embryological factors are essential key factors in tailoring the surgical plan for children [12]. Moreover, pediatric skull base reconstruction presents a unique set of anatomic and technical challenges for the skull base surgeon [13]. As a result, some centers use individualized 3D-printed models to help surgeons gain experience with anatomic limitations characteristic of the pediatric anterior skull base [14] and to enhance patient comprehension

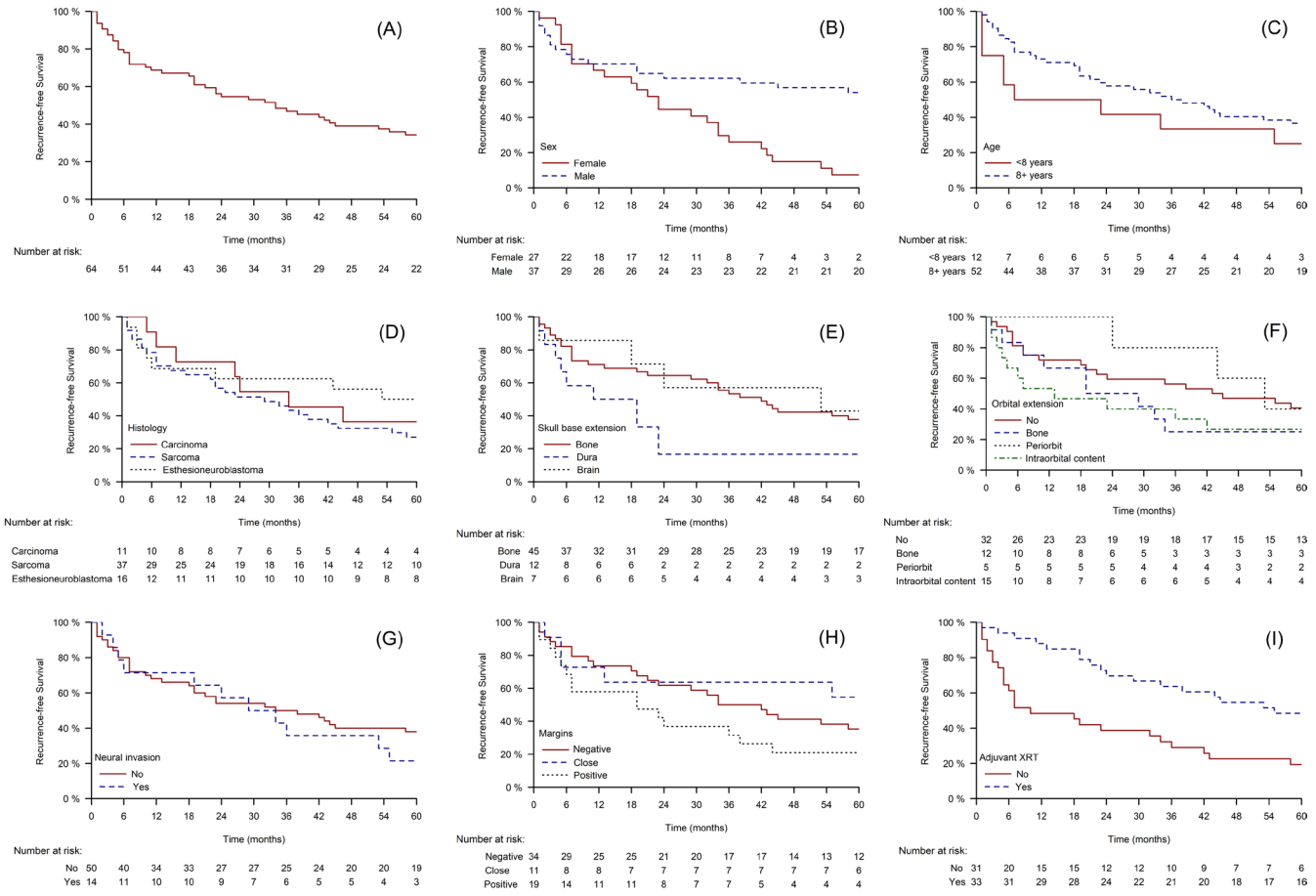

FIGURE 4 | Kaplan–Meier curves for disease-free survival. (A) Disease-free survival for the entire cohort; (B) Sex; (C) Age; (D) Pathology; (E) Skull base invasion; (F) Orbital invasion; (G) Neural invasion; (H) Margins; (I) Adjuvant radiotherapy. [Color figure can be viewed at wileyonlinelibrary.com]

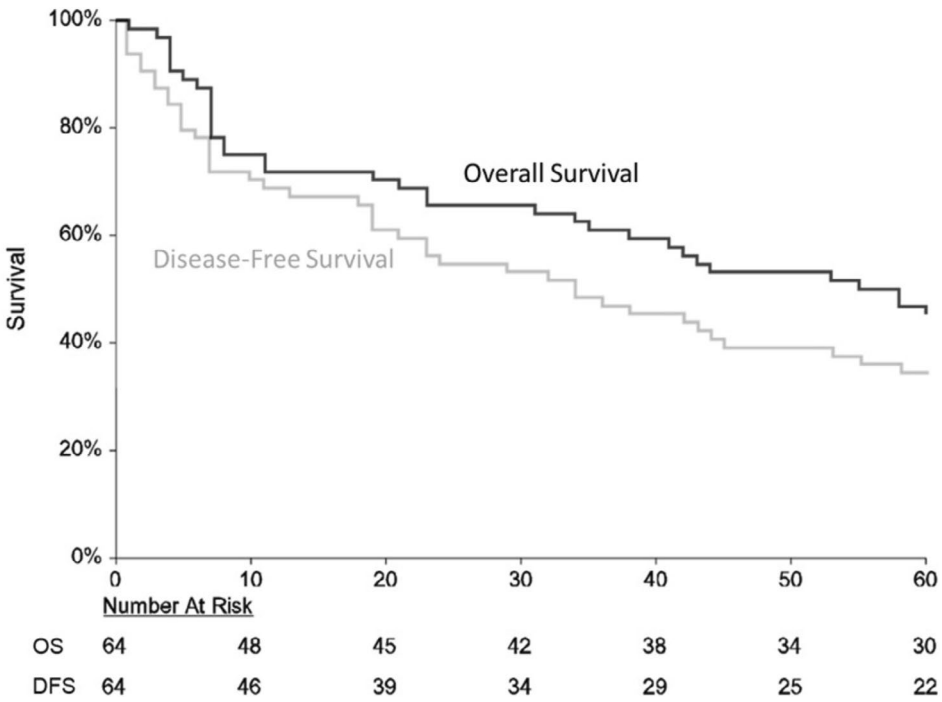

FIGURE 5 | Kaplan–Meier curves for overall and disease-free survivals. DFS, disease-free survival; OS, overall survival.

of the nature of the planned surgery and the potential associated complications [15].

The differences between pediatric and adult skull base surgery derive from several characteristics unique to children and adolescents:

1. The limited space in the anatomy of the pediatric skull base and the proximity of the tumor to critical structures present considerable challenges for safe surgical removal and safe administration of adjuvant radiotherapy, putting these patients at high risk for substantial morbidity and local recurrence, and long-term sequela of treatment.
2. These neoplasms are less common in the pediatric population. The histologic distribution of the tumors is different, with sarcoma being the most common tumor in children. There also are anatomical differences between adults and children due to a growing facial skeleton. These differences translate into greater difficulty in the pediatric sub-population compared to tumor removal in adults
3. Anatomical landmarks are inconsistent in children (e.g., the superior orbital fissure may be absent, the facial nerve will probably be more superficial due to underdevelopment of the mastoid tip).
4. Little is known about the impact of osteotomies and radiation therapy on facial growth and development in the pediatric age group.

Our cohort represents the pediatric sub-population of the 2nd international collaborative study (1995–2015) [4], which represents only 2.2% of the total cohort. This is less than half of the pediatric group described in the 1st international collaborative study (1956–2000), where the pediatric and adolescent population comprised 6.4% (84/1307). While the authors are not sure what the reason for this discrepancy is, we could only speculate that since the peak incidence of skull base malignancies is in the age of 18–21 years [11], excluding these age groups from this study had the benefit of a more homogeneous population, at the expense of a smaller cohort.

Since our cohort was evaluated, treated, and followed in the endoscopic era, we stratified the demographic variables, as well as tumor characteristics and surgical complications as a function of open versus endoscopic approach. In spite of the increasing popularity of endoscopic skull base surgeries in the adult population since the beginning of the 21st century, their application remains primarily limited to tumors confined to the nasal cavity, with or without extension to the paranasal sinuses (ethmoids, maxillary and nasopharynx). These sites accounted for only 76.6% of our current cohort, and exclusively endoscopic-assisted resection and reconstruction were used in the management of 16.3% of them. These data reflect the practice of avoiding endoscopic surgery when skin or orbital contents are invaded by the disease. In addition, the purely endoscopic approach poses a significant technical challenge in children whose nasal aperture and middle corridor are much narrower than in adults. Moreover, sphenoid pneumatization to the planum and sella starts at age 3 years and is completed by age 15 years; both anatomical considerations may rule out an endoscopic approach.

There is still also a lack of specifically designed pediatric surgical instruments suitable specifically for children and adolescents [16]. The open approach is therefore more common when the disease extends to the orbit, skin, PPF, and ITF (59.7% of the cases in the current study). Interestingly, we calculated a high proportion (28.4%) of combined (open and endoscopic) approaches that may represent a transitional era during which the limits of endoscopy appear to be expanding. That said, the 2nd International Collaborative Study (1995–2015) [4] on adults reported a 36% rate of purely endoscopic approaches compared to our 11.9% rate of purely endoscopic approaches in the pediatric population. This may reflect a slow transition of the therapeutic approaches used among adults to their application among children and adolescents.

Endoscopic technology has allowed surgeons to access the skull base through narrow corridors or combined with open approaches. Narrowing the design of endoscopes and the use of fixed angle or adjustable angle endoscopes allows surgeons to view around anatomical corners. The view, improved lighting, and high-definition systems ranging from 1080 to 4 K and specifically designed instrumentation have allowed safe endoscopic surgery to evolve and the conversion from open surgical approaches. Further, other technologies including ultrasound probes, nerve stimulators, fluorescent vascular imaging, image guidance, and evolving 3D technology are employed by some surgeons. This study does not address nor investigate the impact of specific technologies, nor identify which institute uses the various technologies. As the endoscopic approach to the skull base gains greater popularity, even in the context of malignancy, randomized controlled studies comparing endoscopic versus open approaches to matched tumors seem unrealistic.

In contrast to the 4.8% postoperative mortality rate cited in the previous Pediatric International Collaborative study [11], there were no mortalities in the current analysis. Our complication rate, however, was similar to that of earlier studies [3, 11]. That finding might result from expanding the operative candidates to include more surgically complicated cases as technology and expertise improved over time. It is possible that these cases would not have been considered suitable for surgery decades ago.

Free flaps for pediatric skull base reconstruction were performed exclusively in cases of open approaches (50%). Unlike the use of free flaps in only 8% of the cases described in the first international study [11]. We consider that this factor probably contributed to the 0 mortality rate observed in the current study. Free flap transfer for pediatric skull base reconstruction is rare and underreported in the literature. However, application of the vast amount of information that has been documented in adults together with the limited research on pediatric patients can be useful in guiding innovative free flap reconstruction in children [17].

The tumor distribution was in line with that of the first international collaborative study [11] where sarcoma was the most common malignancy. The current collaboration showed a sarcoma rate of over 55% compared to the 40% cited in the previous investigation. This may be attributed to the fact that the latter enrolled patients as old as 21 years, among whom sarcomas

become second to carcinoma in incidence, while we excluded patients older than 18 years at diagnosis.

An interesting finding that warrants investigation is the significantly superior OS and DFS among males. The previous pediatric collaboration [11] did not show the length of OS and DFS as being a function of sex. We have no satisfactory explanation for this observation, although our data showed a similar distribution of the different malignancies between sexes as well as that of perineural invasion, margins status, and staging.

Adjuvant radiotherapy showed significantly improved OS and DFS. These findings are in contrast with the previous pediatric collaboration [11] which showed a non-significant impact of adjuvant radiotherapy on these parameters. This discrepancy may be the result of the continuing development of improved adjuvant radiotherapy techniques.

Skull base extension did have a significant influence on OS. We found that children with dural invasion had worse OS compared to bone and brain invasion, similarly to the finding of the first pediatric skull base collaboration but not discussed at length [11]. While better OS for dural extension compared to brain extension is difficult to explain, we believe that it results from improved adjuvant radio-chemotherapy protocols.

The impact of the surgical approach on the facial skeleton growth during childhood is a vital consideration in our patient population. There has been some concern regarding the undesirable effect of osteotomies on midface development based upon observations on adolescent monkeys following Le Fort I osteotomies [18]. LeFort I osteotomies on humans, however, were not associated with abnormal facial growth and development sequelae [19]. Similar results were observed in a study investigating the effect of nasofrontal orbital osteotomies performed during a subcranial approach in the pediatric population [20]. Facial growth and development disturbances were not observed in our cohort, and we believe that osteotomies which ensure a wide approach to the skull base are safe during childhood.

5 | Study Limitations

Despite the authors' efforts to collect and analyze the data on rare cases worldwide, it should be borne in mind that there are limitations due to its retrospective design based upon medical reports, as well as on a small, heterogeneous cohort and the lack of standardized protocols across institutions. Additionally, even though 64 cases were included, which probably compose the largest case series in the scientific literature in the past 15 years, this number is still small. It is the authors' hope that this publication will contribute to the establishment of a consistently acceptable treatment protocol for these patients. Another limitation that should be kept in mind is the heterogeneity of the pathologies described in these studies. Additionally, some of the malignancies are treated with trimodal therapy, namely chemotherapy, radiation, and surgery. Since neoadjuvant chemotherapy has the potential to alter the extent of surgery in some sinonasal malignancies, it is difficult to compare outcomes across different pathologic types in a relatively small cohort of patients. It should also be noted that overall survival rates for sarcomas depend upon type and may vary widely.

6 | Conclusions

Tumors of the skull base in pediatric patients present a surgical challenge. The results of this recent international collaborative study show that OS was 46.9% at 5 years. Positive independent prognostic factors for OS and DFS were male sex and adjuvant radiation therapy, and 45% of the tumors were diagnosed after the age of 15 years. Sarcoma was the most common type of tumor, with 57.8% of the cases, as opposed to 40% of the cases in the first pediatric collaborative study. The types of carcinoma included mucoepidermoid, adenocarcinoma, and adenoid cystic carcinoma, which accounted for 21.9% of the cases, and none of squamous cell carcinoma. Negative margins were achieved in 53.1% of the children indicating that the achievement of negative margins in this challenging and complicated anatomical location remains a difficult surgical task. In this study, covering the period between 1995 and 2015 open approaches accounted for 59.4% of the cases, combined open and endoscopic approaches for 28.1% of the cases, and purely endoscopic approaches for only 12.5% of the cases, but as Figure 2 shows, by the end of the period covered by this study there is a clear rise in the cases treated by endoscopic or combined approaches. These results probably represent a transitional era in which endoscopic techniques in children have expanded and continue to do so.

Author Contributions

Dan M. Fliss: concept; design; data accrual; analysis; manuscript writing and review. **Omer J. Ungar:** concept; design; data accrual; statistical analysis; graphics; manuscript writing and review. **Helena Levyn:** data analysis. **Cristina Valero:** project development; data monitoring and transfer; analysis; manuscript preparation; review. **Dauren Adilbay:** project development; data monitoring; data transfer; data accrual; analysis. **Alana Eagan:** project development; data monitoring; data transfer; analysis. **Junting Zheng:** statistical analysis. **Mithat Gonen:** statistical analysis. **Marc Cohen:** data contribution; manuscript review. **Snehal Patel:** project development; data monitoring and transfer; analysis; manuscript review. **Ian Ganly:** data contribution. **Prathamesh Pai:** data contribution and transfer. **Paolo Castelnuovo:** data contribution and transfer. **Fang Ju Gao:** data contribution and transfer. **Cesare Piazza:** data contribution and transfer. **Piero Nicolai:** data contribution and transfer. **Ben Panizza:** data contribution and transfer. **James Bowman:** data contribution and transfer. **Catherine Barnett:** data contribution and transfer. **Luiz P. Kowalski:** data contribution and transfer. **Ronaldo Toledo:** data contribution and transfer. **John DeAlmeida:** data contribution and transfer. **Ian Witterick:** data contribution and transfer. **Philippe Herman:** data contribution and transfer. **Walter Fontanella:** data contribution and transfer. **Gregorio Sanchez Aniceto:** data contribution and transfer. **Sefik Hosal:** data contribution and transfer. **Serdar Ozer:** data contribution and transfer. **Subramania Iyer:** data contribution and transfer. **Richard Harvey:** data contribution and transfer. **C. Rene Leemans:** data contribution and transfer. **Jan-Jaap Hendrickx:** data contribution and transfer. **Marcelo Figari:** data contribution and transfer. **Luis Boccalatte:** data contribution and transfer. **Ken Ichi Nibu:** data contribution and transfer. **Peter Clarke:** data contribution and transfer. **Catherine Rennie:** data contribution and transfer. **Zhu Yi Ming:** data contribution and transfer. **Claudio Cernea:** data contribution and transfer. **Sergio Goncalves:** data contribution and transfer. **Rodney Schlosser:** data contribution and transfer. **Fernando Dias:** data contribution and

transfer. **Zoukaa Sargi:** data contribution and transfer. **Shahzada Ahmed:** data contribution and transfer. **Wojciech Golusinski:** data contribution and transfer. **Se Heon Kim:** data contribution and transfer. **Shirley Y. Su:** data and manuscript review. **Shaan M. Raza:** data and manuscript review. **Franco DeMonte:** data and manuscript review. **Ehab Hanna:** data contribution and transfer. **Jatin P. Shah:** concept; design; data accrual; manuscript review.

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Ethics Statement

Each contributing center has local institutional approval. This is an original manuscript reviewed by all authors and not under consideration for publication elsewhere.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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