

Skull base surgery for malignant tumors: The 2nd international collaborative study (1995–2015)

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Abstract

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

Patients and methods: A total of 28 institutions contributed data on 3061 patients. Analysis evaluated clinical variables, survival outcomes, and multi-variable factors associated with outcomes.

Results: The median age was 56 years (IQR 44–67). The open surgical approach was used in 55% ($n = 1680$) of cases, endoscopic resection was performed in 36% ($n = 1087$), and the combined approach in 9.6% ($n = 294$). With a median follow-up of 7.1 years, the 5-year OS DSS and RFS were 65%, 71.7% and 53%, respectively. On multivariable analysis, older age, comorbidities,

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histology, dural/intracranial involvement, positive margins, advanced stage, and primary site were independent prognostic factors for OS, DSS, and RFS. Adjuvant RT was a protective prognostic factor.

Conclusion: The progress across various disciplines may have contributed to improved OS and DSS in this study compared to previous reports.

KEYWORDS

global collaboration, multimodality treatment, prognostic factors, skull base tumors, survival outcomes

1 | INTRODUCTION

The pioneering work of Ketcham to surgically remove malignant tumors of the paranasal sinuses approaching or involving the anterior skull base opened the doors for surgical resection of these difficult tumors.¹ Over the next four decades investigators reported modifications and improvements in surgical techniques, reporting individual or institutional series for a variety of benign and malignant tumors of the skull base.^{2–7} Despite the widespread acceptance of en bloc resection, the seminal publications on endoscopic surgical techniques by Jankowski, Carrau, and Stammberger^{8–10} challenged the open en bloc surgical resection concept and led to the introduction of completely endoscopic and combined endoscope-assisted techniques for tumors localized to the anterior central skull base. However, given the rarity of skull base cancer,¹¹ none of the reported series had sufficient number of malignant tumors to stratify their data to report outcomes related to histology, stage of the disease, and the extent of involved structures. In an attempt to overcome these limitations, Shah and colleagues joined forces with collaborators from 17 institutions worldwide to establish a benchmark for treatment outcomes.¹² This study, published in 2003, analyzed 1307 patients who underwent craniofacial resection, and reported 5-year overall, disease-specific, and recurrence-free survival rates of 54%, 60%, and 53%, respectively. In addition, it identified independent factors impacting outcomes, such as histology, stage of disease, margin status, and extent of intracranial extension.

The last two decades have seen enormous progress, including the availability of high-resolution imaging modalities, widespread adoption of endoscopic techniques and intraoperative navigation systems, introduction of neoadjuvant therapies and adjuvant systemic treatments, and novel microvascular reconstruction options.^{13–18} In light of continuous progress made by all disciplines involved in the treatment of skull base tumors, here we present the joint endeavor of 28 institutions across the globe with a combined cohort of 3061 patients, treated between 1995 and 2015, to report

current outcomes for malignant tumors involving the anterior and middle fossa skull base, undergoing surgical resection.

2 | METHODS

2.1 | Patient selection

All major institutions and or investigators who had reported their experience in skull base surgery in the literature were identified through PubMed search and subsequently approached to contribute their data for a large collaborative international study. Data transfer agreements were executed between Memorial Sloan Kettering Cancer Center (MSK) and each organization's institutional review board (IRB) to comply with patient privacy regulations. The inclusion criteria were patients who underwent skull base surgery for a malignant tumor between 1995 and 2015. A total of 28 institutions participated in the study. From an initial cohort of 3379 patients, 318 (9.4%) were excluded during the data auditing phase due to not meeting all the inclusion criteria, missing data on required fields, or being duplicates or “test” entries.

After exclusions, 3061 patients were eligible for the study. Out of the 28 participating institutions, 8 were from Asia (948 patients; 31.0%), 2 from Australia (171 patients; 5.6%), 9 from Europe (877 patients; 28.7%), 5 from North America (820 patients; 26.8%), and 4 from South America (245 patients; 8.0%) (see Figure S1, Supporting Information). The list of collaborating institutions is shown in Table S1.

2.2 | Data entry, audit, and analysis

After signing a Data Transfer Agreement (DTA), each collaborator was sent a specific link for entering the data into a standard database template. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at

MSK.^{19,20} Data analysis was performed in a centralized fashion in the Department of Biostatistics at MSK.

2.3 | Statistical methods

Patient demographics, disease characteristics, and treatment variables were summarized in median (interquartile range, IQR) and percent. The Pearson's chi-square test, the Wilcoxon rank sum test, and the Fisher's exact test were used to evaluate associations between surgical approach and other clinical variables. The Kaplan–Meier method was used to estimate overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS). For OS, patients were censored if they were alive at the last clinical follow-up; when the latter was not available, they were censored at the date of last contact. For the calculation of RFS, patients who were alive without local, regional, or distant metastasis were censored at the date of last clinical follow-up. In order to compare the results to the first international study published in 2003, we provided DSS estimations by censoring patients who died of other causes at the time of death, while acknowledging that this survival analysis approach would overestimate the probability of cancer-specific death (CSD) in which we treated death due to other causes as a competing event.

Local, regional, and distant recurrence-free probabilities were simply estimated in all patients using the Kaplan–Meier method censoring event-free patients at the last follow-up. The log-rank test and the Gray's test were used to assess univariable associations between clinical variables and survival outcomes.

A weighted Cox regression model proposed by Schemper et al.²¹ was used to analyze multivariable associations with OS, DSS, and RFS. This model was adopted instead of the proportional hazard Cox regression because several clinical variables did not satisfy the proportional hazards assumption. The weighted Cox regression model estimates weighted average hazard ratios which can be interpreted as an averaged hazard ratios over the entire follow-up time weighted by survival and censoring probabilities at each time point.

Multivariable survival analyses started with univariately significant variables in OS, DSS, and RFS, applied a backward variable selection approach based on the Wald test. The stay *p*-value was set at 0.05. Patients with unknown/other orbital involvement or intracranial involvement were removed considering small numbers of unknowns.

For model stability, the time range was limited to 15 years from surgery considering only <1.5% events (death) were observed afterwards. Patients with events after 15 years were censored at the time.

All statistical analyses were performed using software packages R version 4.2.2 (The R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Patient and tumor characteristics

Patient characteristics are shown in Table 1 and Figure 1. The median age was 56 years (Interquartile [IQR] 44–67) and 64% of the patients were male. The median Karnofsky score was 90 (IQR 90–100). Tumor clinical characteristics are listed in Table 2. Most patients (75%) were treated for a primary tumor, with the ethmoid sinuses being the most common tumor location (34%, *n* = 1041), followed by the nasal cavity (23%, *n* = 699), and the maxillary sinus (21%, *n* = 654). As for staging, 60% of the cases were considered pT4, and 82% were staged as pT3–pT4, per AJCC 8th Ed.

The most common histology was squamous cell carcinoma (SCC), which accounted for 28% of the cases (*n* = 867), followed by adenocarcinoma in 15% (*n* = 469) and esthesioneuroblastoma (ENB) in 12% (*n* = 357). The distribution of the histologic type is shown in Figure 2.

TABLE 1 Patient characteristics.

Characteristic	N = 3061 ^a
Age, years	56 (44, 67), [1, 98]
Age group, years	
<20	87 (2.8%)
20–40	448 (15%)
40–70	1903 (62%)
>70	623 (20%)
Sex	
Female	1107 (36%)
Male	1954 (64%)
Medical comorbidities	
No	1397 (46%)
Yes	1043 (34%)
Unknown	621 (20%)
Karnofsky score	90 (90, 100), [40, 100]
Karnofsky score by group	
<80	68 (4.4%)
80–90	861 (56%)
100	603 (39%)
Not available	1529

^aMedian (IQR), [range]; *n* (%).

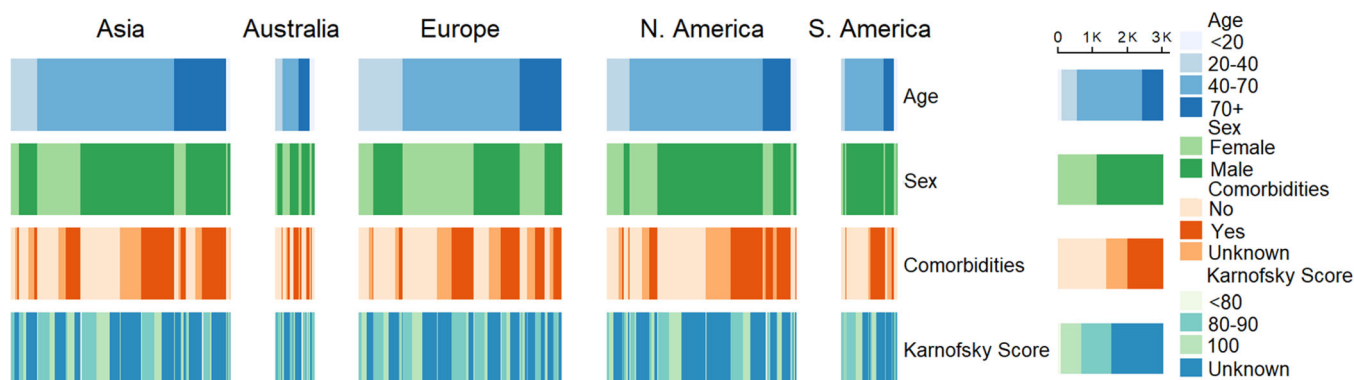


FIGURE 1 Oncoprint of patient demographics.

The histologic distribution per primary tumor site varied significantly for each primary site as shown in Figure S2. For example, in ethmoid tumors, a higher percentage of adenocarcinomas (30.3%) were noted, while in tumors that originated in the infratemporal fossa salivary gland tumors and sarcomas were most frequent (38.3% for both), and in the nasal cavity a variety of different histologies were seen (9%–20%).

3.2 | Treatment information

The open surgical approach was used in 55% ($n = 1680$) of cases, endoscopic resection was performed in 36% ($n = 1087$) of cases and the combined open and endoscope-assisted approach in 9.6% ($n = 294$) (Table 3). Most patients had an anterior skull base resection only (80%), and 72% underwent reconstruction of some sort. Negative or close margins were achieved in 66% of resections.

The distribution of tumor site, histology, and margins based on the surgical approach (open vs. endoscopic vs. combined) is shown in Table S2. Most endoscopic and combined approach surgeries were carried out for tumors originating in the ethmoid sinuses and the nasal cavity. The most common primary tumor site for the open surgical approach was the maxillary sinus. The highest rate of positive resection margins was observed in the open approach (32%, $n = 532$), followed by the combined open endoscope-assisted approach (25%, $n = 74$). The pure endoscopic approach had the lowest rates of positive margins (18%, $n = 201$).

Open procedures were more commonly used for recurrent tumors (31% vs. 18% in the endoscopic/combined approaches), advanced T stages (70% were staged T4 compared to 48%), for tumors involving the middle fossa (18% vs. 4.2%), the orbit (28% vs. 6.9%), and tumors causing cranial nerve deficits (26% vs. 7.5%, $p < 0.001$) (Table S3).

Detailed information about the type of reconstruction for different extents of skull base resections is shown in Table 4 and Table S5. A higher rate of patients with T4 stage tumors and patients who underwent open surgical approach required reconstruction (67% and 64%, respectively) (Table S4). Overall, the most common type of reconstruction was a free flap which was carried out in 22% of cases. For anterior fossa resections, the preferred reconstruction method was a galeal pericranial flap (23%), while in middle fossa resections, a free flap was most commonly used (40%). In cases in which the resection encompassed both anterior and middle fossa, again the free flap was the most common type of reconstruction (55%).

Overall, 66% ($n = 2022$) patients had histopathologically proven tumor invasion of the anterior fossa or middle fossa or both Table S6. In patients who had anterior fossa resections, 62% had histopathologic evidence of tumor invasion of the anterior skull base. In the group of patients with middle fossa resection, 81% had tumor invasion of the lateral skull base. Of those with anterior and middle fossa resections, 72% had invasion of both sites, 10% had anterior skull base invasion only, and 5% had invasion limited to middle fossa skull base.

3.2.1 | Complications

Thirty-one percent of patients had at least one postoperative complication (Table 5), the most common being local infection (5.5%, $n = 169$) and cerebrospinal fluid (CSF) leak (5.3%, $n = 163$). The rates of complications were higher in open and combined approaches compared to purely endoscopic procedures (38% and 42% vs. 16%, respectively). Postoperative mortality was reported in 42 cases (1.4%), mainly in association with the open surgical approach ($n = 38$; 90% of the postoperative deaths). For the endoscopic approaches (either pure-endoscopic or combined), CSF leak was the most commonly

TABLE 2 Tumor characteristics.

Characteristic	N = 3061 ^a
Tumor type	
Primary	2302 (75%)
Recurrent	759 (25%)
Tumor primary site	
Ethmoid sinus	1041 (34%)
Nasal cavity	699 (23%)
Maxillary sinus	654 (21%)
Skin	217 (7.1%)
Orbit	67 (2.2%)
Infratemporal fossa	47 (1.5%)
Lacrimal gland	17 (0.6%)
Pterygoid fossa	17 (0.6%)
Other	302 (9.9%)
Skull base invasion	
None	1039 (34%)
Anterior fossa	1527 (50%)
Middle fossa	357 (12%)
Both	138 (4.5%)
Histologic type	
Squamous cell carcinoma	867 (28%)
Adenocarcinoma	469 (15%)
Esthesioneuroblastoma	357 (12%)
Salivary gland	325 (11%)
Sarcoma	303 (9.9%)
Melanoma	202 (6.6%)
Basal cell carcinoma	76 (2.5%)
Other	462 (15%)
pT classification AJCC 8th ed	
1	113 (3.7%)
2	282 (9.2%)
3	669 (22%)
4	1830 (60%)
Unknown	167 (5.5%)
Orbital involvement	
No	1806 (59%)
Periosteum/bone	624 (20%)
Intraorbital contents	568 (19%)
Others	63 (2.1%)
Intracranial involvement	
No	1342 (44%)
Bone	944 (31%)
Dura	556 (18%)

(Continues)

TABLE 2 (Continued)

Characteristic	N = 3061 ^a
Brain	208 (6.8%)
Others	11 (0.4%)
Cranial nerve deficits	546 (18%)
Skin tumor extension	310 (10%)

^an (%).

observed complication (3.8% and 7.5%, respectively), while local infection was the most common complication noted in the patients undergoing resection through an open approach (9.3%, $n = 156$).

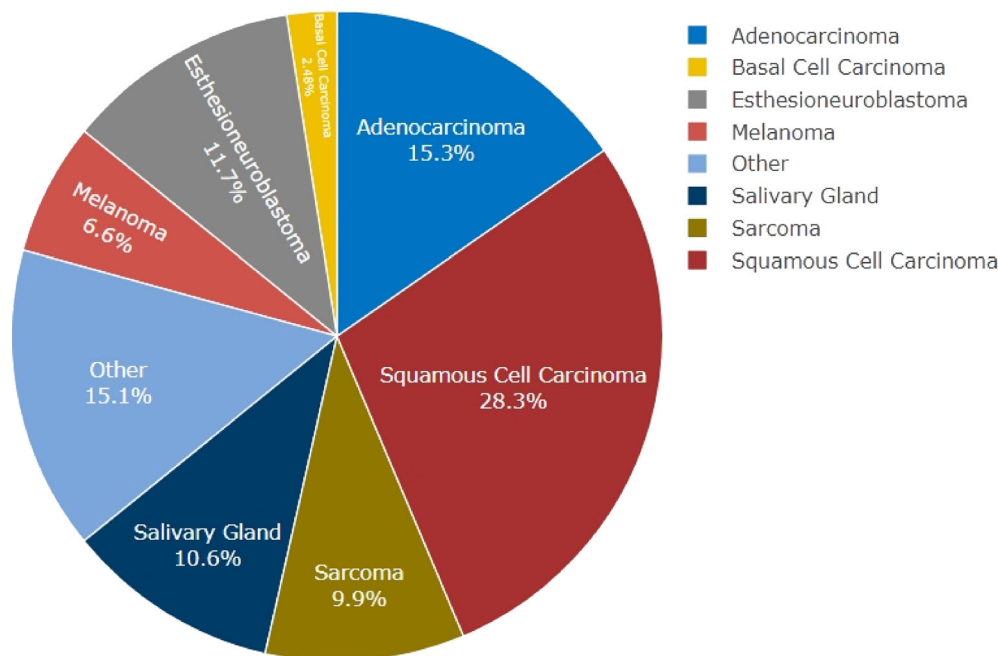
3.2.2 | Prior, neoadjuvant, and adjuvant treatment

Information about prior skull base cancer related treatment, neoadjuvant treatment and adjuvant treatment can be found in Table 6. A total of 38% of the patients had treatment prior to skull base resection, mainly some type of prior surgery (32%). Neoadjuvant chemotherapy was administered in 10% ($n = 309$) of patients, <0.1% ($n = 3$) received neoadjuvant immunotherapy, and 1.9% had other treatments. Most patients received postoperative adjuvant therapy (70%): 52% received adjuvant radiotherapy, 12% received chemoradiotherapy, and 4.7% other types of combinations.

Figure 3 demonstrates the KM curves for OS, DSS, and RFS by treatment group. Adjuvant RT with or without any prior or neoadjuvant treatment, was associated with a higher 5-year OS (70%, 67%–73% CI) compared to surgery alone (66%, 61%–71% CI) or adjuvant CRT with or without prior or neoadjuvant treatment (57% and 56%, respectively, $p < 0.001$). Five-year DSS was highest among patients who received adjuvant RT without prior/neoadjuvant treatment (77%, 74%–80% CI) and patients who got surgery alone (75%, 71%–80% CI, $p < 0.001$). Five-year RFS was highest among patients who received adjuvant RT with or without prior/neoadjuvant treatment (59% and 60%, respectively, $p < 0.001$).

A summary of the main patient, tumor, and treatment characteristics for primary versus recurrent tumors is shown in Table S7. While the majority of tumors in both groups arose from either the nasal cavity or ethmoid or maxillary sinuses (83% of primary tumors and 63% of recurrent tumors), a larger proportion of recurrent tumors were of skin origin (14% of recurrent tumors vs. 8.4% of primary tumors). Primary tumors were more often adenocarcinomas (17% vs. 10% recurrent tumors), while recurrent tumors were more often squamous cell

FIGURE 2 Distribution of histology.



carcinomas (36% vs. 26% in primary tumors). In comparison to primary tumors, recurrent tumors were more likely to be staged as pT4 (57% vs. 67%), have orbital involvement (39% vs. 47%), and present with cranial nerve deficits (14% vs. 28%). A higher rate of recurrent tumors were treated with the open approach compared to endoscopic resection (68% vs. 51%).

3.3 | Survival outcomes

With a median postoperative follow-up of 7.1 years (95% CI: 6.8–7.4, range: 1 day–24.7 years), the 5-year OS and DSS were 65% (95% CI: 63–67%) and 71.7% (95% CI: 70–73.5%), respectively (Figures 4 and 5). The OS by tumor characteristics and treatment type is shown in Figure S3. The 5-year cumulative incidence rate (CIR) of Cancer Specific Death (CSD) was 27.3% (95% CI: 25.6–29%) (Figures S4 and S5).

Recurrent disease after skull base surgery occurred in 1343 patients (43.9%). The median time to recurrence was 1.7 years (IQR: 0.7, 4.6) and the 5-year RFS was 53% (95% CI: 52–55%). The 5-year local, regional, and distant recurrence-free probability were 68% (95% CI: 66–70%), 91% (95% CI: 90–92%), and 79% (95% CI: 77–81%), respectively (Figure 6). The RFS by tumor characteristics and treatment type is shown in Figure S6.

On multivariable analysis, older age, comorbidities, histologic type, dural/intracranial tumor involvement, positive margins, advanced pT stage, and maxillary sinus primary site were independent prognostic factors for OS, DSS, and RFS. Adjuvant RT with or without any prior or

TABLE 3 Surgical characteristics and extent of surgery.

Characteristic	N = 3061 ^a
Approach	
Endoscopic	1087 (36%)
Open	1680 (55%)
Combined/endoscopically assisted	294 (9.6%)
Skull base resection	
Anterior fossa	2442 (80%)
Middle fossa	427 (14%)
Both	192 (6.3%)
Structures resected	
Orbit	1091 (36%)
Maxilla	1541 (50%)
Nasal cavity	2030 (66%)
Bone/cribiform plate	1843 (60%)
Skin	396 (13%)
Brain	222 (7.3%)
Ethmoid	2302 (75%)
Other	1126 (37%)
Tracheostomy performed	309 (10%)
Reconstruction performed	2218 (72%)
Margins	
Negative/close	2025 (66%)
Positive	807 (26%)
Unknown	229 (7.5%)

^an (%).

TABLE 4 Type of reconstruction based on skull base resection.

	Overall, <i>N</i> = 3061 ^a	Extent of resection		
		Anterior fossa, <i>N</i> = 2442 ^a	Middle fossa, <i>N</i> = 427 ^a	Both, <i>N</i> = 192 ^a
Type of reconstruction	2218 (72%)	1706 (70%)	347 (81%)	165 (86%)
Fascia lata	127 (4.1%)	108 (4.4%)	10 (2.3%)	9 (4.7%)
Skin graft	202 (6.6%)	113 (4.6%)	72 (17%)	17 (8.9%)
Free flap	688 (22%)	412 (17%)	170 (40%)	106 (55%)
Alloplastic material	360 (12%)	279 (11%)	49 (11%)	32 (17%)
Nasoseptal flap	139 (4.5%)	111 (4.5%)	20 (4.7%)	8 (4.2%)
Galeal pericranial flap	648 (21%)	552 (23%)	50 (12%)	46 (24%)
Other	942 (31%)	746 (31%)	146 (34%)	50 (26%)

^a*n* (%).**TABLE 5** Postoperative complications.

	Surgical approach			
	Overall, <i>N</i> = 3061 ^a	Endoscopic, <i>N</i> = 1087 ^a	Open, <i>N</i> = 1680 ^a	Combined/endoscopically assisted, <i>N</i> = 294 ^a
Any complications	915 (31%)	162 (16%)	635 (38%)	118 (42%)
Not available	78	43	25	10
Complication type				
Mortality	42 (1.4%)	2 (0.2%)	38 (2.3%)	2 (0.7%)
Acute bleeding	50 (1.6%)	15 (1.4%)	31 (1.8%)	4 (1.4%)
Hematoma	85 (2.8%)	9 (0.8%)	67 (4.0%)	9 (3.1%)
CSF leak	163 (5.3%)	41 (3.8%)	100 (6.0%)	22 (7.5%)
Epidural abscess	15 (0.5%)	3 (0.3%)	9 (0.5%)	3 (1.0%)
Local infection	169 (5.5%)	4 (0.4%)	156 (9.3%)	9 (3.1%)
Systemic infection	55 (1.8%)	7 (0.6%)	46 (2.7%)	2 (0.7%)
Meningitis	42 (1.4%)	7 (0.6%)	24 (1.4%)	11 (3.7%)
Pneumocephalus	57 (1.9%)	8 (0.7%)	36 (2.1%)	13 (4.4%)
Other	570 (19%)	97 (8.9%)	397 (24%)	76 (26%)

^a*n* (%).

neoadjuvant treatment was associated with better OS, DSS, and RFS. Additionally, orbital involvement was an independent prognostic factor of OS and RFS (Table 7). There are geographic variances in primary site location as well as histology (Table S8). For example, skin cancer is more prevalent in Australia and South America, and basal cell carcinoma is a predominant histology in South America. Similarly, adenocarcinoma is more common in Europe, compared to the rest of the world.

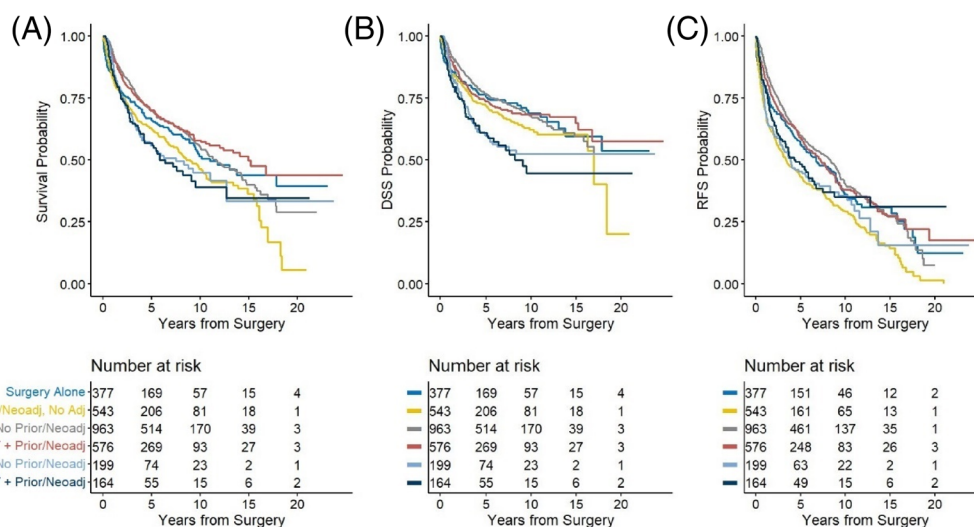
4 | DISCUSSION

Given the rarity of skull base tumors, their high stage at presentation, and their impact on patient survival, there

is a pressing need for large-scale studies on this topic. The present study builds upon the previous international collaborative effort in the field of skull base surgery for malignant tumors.¹² While the previous study examined a cohort of 1307 patients treated between 1956 and 2000, our current endeavor encompasses 3061 patients treated between 1995 and 2015 in 28 academic institutions from five continents. Over the intervening years, the field has seen significant advances in several areas, including imaging technology, neoadjuvant therapies, development of endoscopic instrumentation and techniques, intra-operative navigation, intensive care units equipped with cutting-edge technology, standardized postoperative infection prevention protocols, and enhanced precision radiotherapy and chemotherapy.^{13,14,16,17,22} This study

TABLE 6 Prior treatment, neoadjuvant treatment, and adjuvant treatment.

Prior treatment		Neoadjuvant treatment		Adjuvant treatment		Combinations of treatments	
Any	1148 (38%)	Any	309 (10%)	Any	2098 (70%)	Surgery alone	377 (13%)
Surgery	990 (32%)	Chemotherapy	309 (10%)	Radiotherapy	1955 (65%)	Prior/neoadjuvant therapy, no adjuvant therapy	543 (18%)
Radiotherapy	442 (14%)	Immunotherapy	3 (<0.1%)	Chemotherapy	456 (15%)	Adjuvant RT, no prior/neoadjuvant therapy	963 (32%)
Chemotherapy	227 (7.4%)	Other	57 (1.9%)	Immunotherapy	27 (0.9%)	Adjuvant RT, with prior/neoadjuvant therapy	576 (19%)
Immunotherapy	9 (0.3%)			Other	53 (1.8%)	Adjuvant CRT, no prior/neoadjuvant therapy	199 (6.7%)
Other	13 (0.4%)					Adjuvant CRT, with prior/neoadjuvant therapy	164 (5.5%)



Treatment Group	5-year OS (95%CI)	5-year DSS (95%CI)	5-year RFS (95%CI)
Surgery Alone	66% (61%, 71%)	75% (71%, 80%)	56% (51%, 62%)
Prior/Neoadj, no Adj	63% (58%, 67%)	72% (68%, 76%)	43% (39%, 48%)
Adj RT, no Prior/Neoadj	70% (67%, 73%)	77% (74%, 80%)	60% (57%, 63%)
Adj RT + Prior/Neoadj	70% (66%, 74%)	74% (70%, 78%)	59% (55%, 63%)
Adj CRT, no Prior/Neoadj	56% (49%, 64%)	60% (53%, 68%)	45% (39%, 53%)
Adj CRT + Prior/Neoadj	57% (49%, 66%)	61% (53%, 70%)	48% (41%, 57%)
p Value (Overall)	<0.001	<0.001	<0.001

FIGURE 3 Overall survival (A), disease-specific survival (B), and recurrence-free survival (C) curves comparing patients undergoing surgery alone vs. combinations of prior/neoadjuvant and radiotherapy (RT) and chemoradiotherapy (CRT) adjuvant treatment. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/hed.27746)]

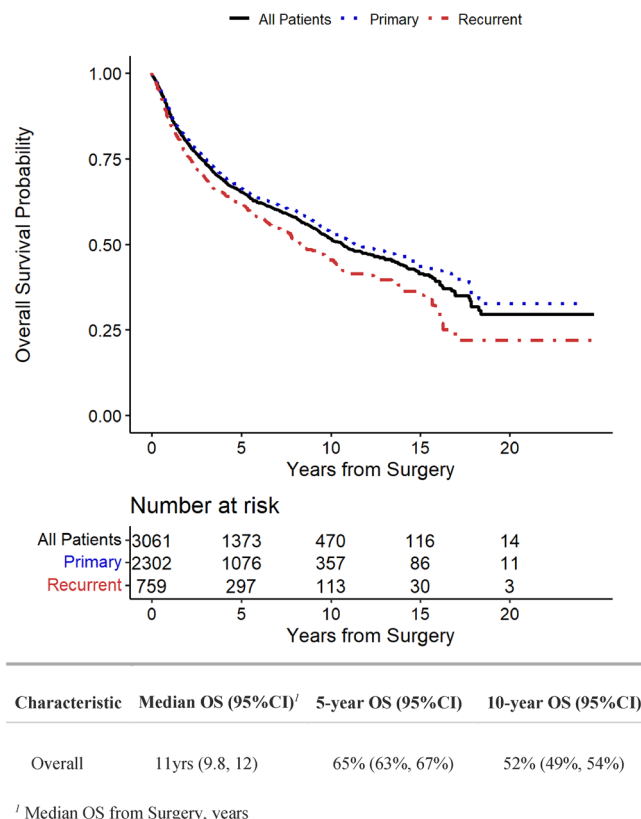


FIGURE 4 Overall survival curves across entire cohort, primary, and recurrent tumors. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

provides a unique opportunity to assess the impact of these advancements on the outcomes of surgically managed skull base tumors, and create a benchmark that can be used to report contemporary outcomes around the globe.

The collaborative endeavor was not without its challenges and hurdles, many of which were influenced by the increasing pressure of regulatory requirements from each participating institution and prevailing circumstances. In contrast to the first international collaborative study, which relied on manual data collection using paper data-sheets, our current study benefited from the development of a unified, secure web platform for streamlined data collection and analysis. However, achieving this milestone required extensive communication and negotiations involving legal teams from 28 institutions. Overcoming this considerable obstacle demanded the genuine commitment and dedication of leaders from all institutions, driven by their shared vision of advancing high-quality research in this domain. In spite of these concerted efforts it took nearly 2 years to comply with all legal documents between each participating institution/investigator and the central data repository at MSK, before statistical analyses could commence.

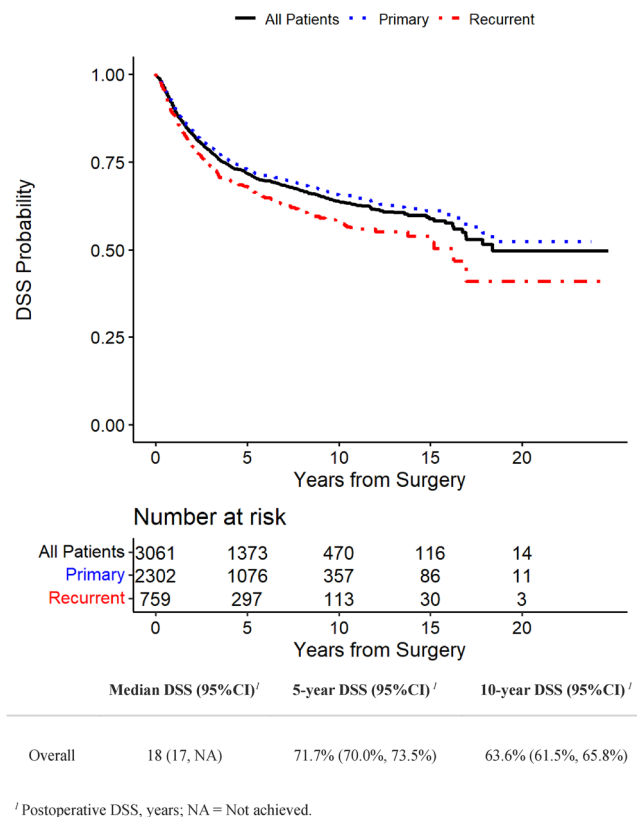


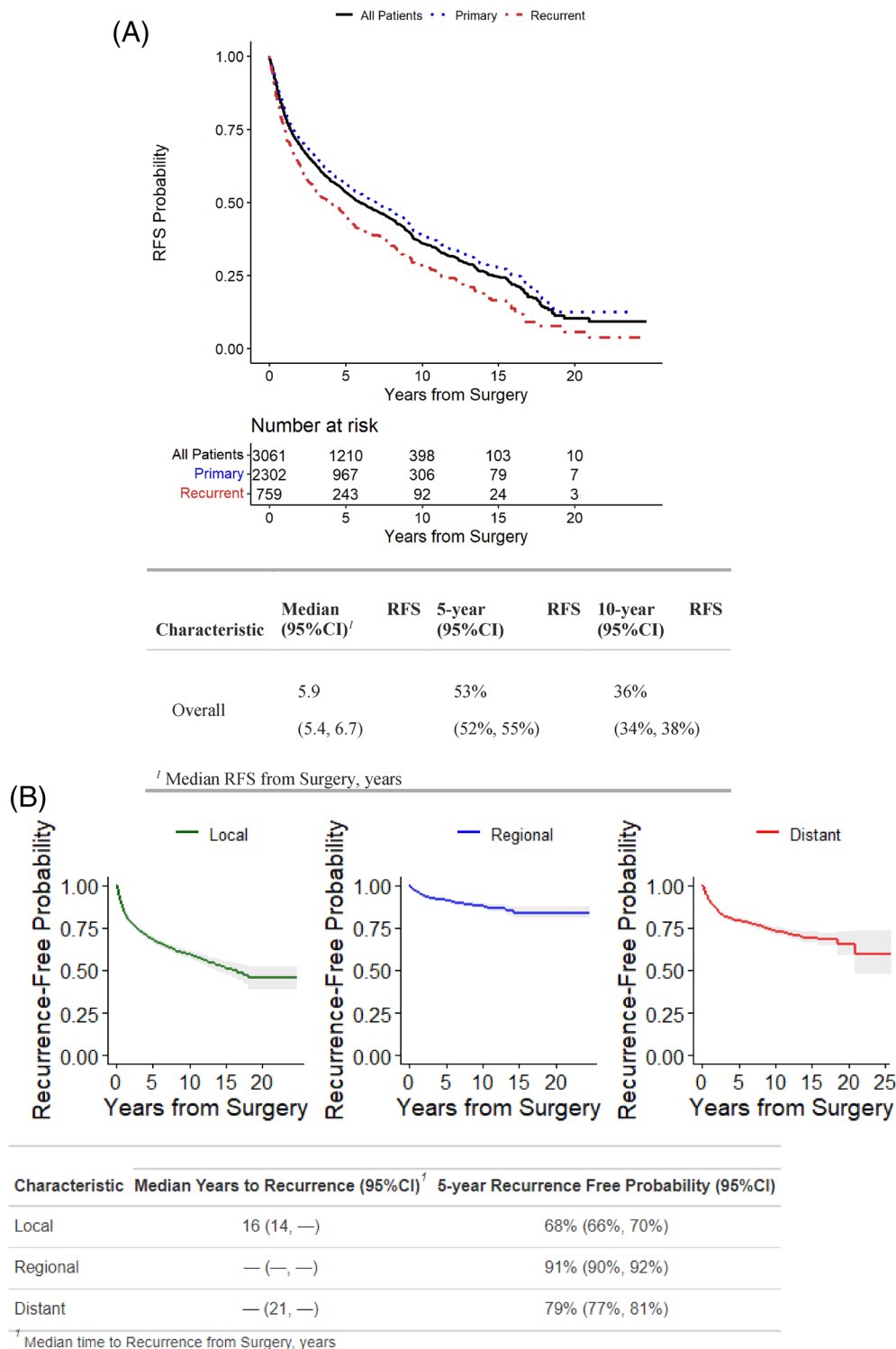
FIGURE 5 Disease-specific survival curves across entire cohort, primary, and recurrent. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

An intriguing finding of our study is that the general distribution of different tumor histologies involving the skull base has remained remarkably similar to the previous report.¹² Specifically, SCC accounted for 28% of cases ($n = 867$, 28.8% in the previous study), followed by adenocarcinoma in 15% ($n = 469$, 16% in the previous study) and ENB in 12% ($n = 375$, 11.6% in the previous study). This stability is particularly notable given the decreasing rates of smoking in the Western world since the 1950s, suggesting that environmental factors may have only a limited impact on the histologic distribution of malignancies involving the skull base.

Our study suggests that despite the increasing popularity of endoscopic skull base surgeries over the last two decades, their utility remains primarily limited to tumors of the ethmoid sinuses, nasal cavity, and to a lesser extent, the maxillary sinus. Collectively, these three sites accounted for 91.8% of surgeries carried out using a purely endoscopic approach. Conversely, the open surgical approach was more commonly employed for a higher proportion of maxillary sinus tumors (31%, compared to 8.8% with the endoscopic approach) as well as tumors arising from the skin (13%), infratemporal fossa (2.4%), and orbit (3.7%).

Given the retrospective nature of this study, it is imperative to acknowledge that the higher rates of

FIGURE 6 Recurrence-free survival (RFS) curves across entire cohort, primary, and recurrent tumors (A), and local, regional and distant recurrence-free probability curves (B). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/hed.27746)]



postoperative mortality, positive margins, and resulting adverse impact on OS observed in the open surgical approach is most likely attributed to selection bias. Our results show that the open approach was more commonly used for recurrent tumors and advanced disease, and often presented in areas of higher anatomical complexity.

The use of adjuvant therapy following skull base surgery has notably increased from that reported in the previous collaborative study, where only 39% of patients underwent

postoperative radiation therapy (PORT), as the current data demonstrates a rise to 65% ($n = 1955$). Similarly, the administration of adjuvant chemotherapy (CT) has also increased substantially, with only 4.4% of patients receiving this therapy in the previous study, compared to 15% of patients receiving adjuvant CT ($n = 456$) and 12% receiving adjuvant concurrent chemoradiotherapy (CRT) in the current study ($n = 371$).

The preceding multinational research endeavor notably omitted any reference to endoscopic surgical

TABLE 7 Multivariable analyses for overall survival, disease-specific survival, and recurrence-free survival.

Variables	OS			DSS			RFS		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age, years									
≤50	Ref			Ref			Ref		
>50	1.55	1.33–1.81	<0.001	1.22	1.02–1.46	0.030	1.21	1.07–1.37	0.003
Comorbidities									
No	Ref			Ref			Ref		
Yes	1.30	1.12–1.52	<0.001	1.23	1.02–1.48	0.028	1.14	1.00–1.28	0.044
Unknown	1.29	1.08–1.54	0.005	0.97	0.77–1.21	0.766	1.25	1.08–1.45	0.003
Histology									
Esthesioneuroblastoma	Ref			Ref			Ref		
Adenocarcinoma	2.06	1.52–2.78	<0.001	1.85	1.25–2.75	0.002	1.46	1.18–1.79	<0.001
Basal cell carcinoma	1.97	1.13–3.42	0.017	0.75	0.30–1.88	0.540	1.19	0.76–1.86	0.448
Melanoma	5.40	3.90–7.48	<0.001	7.89	5.26–11.84	<0.001	3.60	2.83–4.58	<0.001
Salivary gland	1.57	1.13–2.18	0.007	2.22	1.42–3.47	<0.001	1.28	1.03–1.59	0.028
Sarcoma	1.73	1.22–2.46	0.002	2.02	1.31–3.13	0.002	1.26	0.98–1.63	0.073
Squamous cell	2.29	1.71–3.05	<0.001	2.43	1.66–3.56	<0.001	1.47	1.20–1.80	<0.001
Other	2.06	1.51–2.82	<0.001	2.38	1.58–3.58	<0.001	1.38	1.11–1.71	0.004
Intracranial involvement									
No	Ref			Ref			Ref		
Bone	1.18	1.01–1.37	0.038	1.10	0.90–1.34	0.366	1.10	0.97–1.25	0.121
Dura	1.35	1.11–1.63	0.002	1.45	1.15–1.83	0.002	1.43	1.23–1.66	<0.001
Brain	1.73	1.29–2.32	<0.001	2.10	1.53–2.88	<0.001	1.60	1.25–2.05	<0.001
Margins									
Negative/close	Ref			Ref			Ref		
Positive	1.84	1.59–2.12	<0.001	2.11	1.78–2.49	<0.001	1.77	1.57–1.99	<0.001
Unknown	1.25	0.98–1.61	0.077	1.19	0.87–1.61	0.278	1.55	1.28–1.88	<0.001
Orbital involvement									
No	Ref						Ref		
Periosteum/bone	1.23	1.05–1.44	0.011				1.29	1.13–1.48	<0.001
Intraorbital contents	1.23	1.03–1.48	0.023				1.29	1.11–1.50	<0.001
pT stage AJCC 8th edition									
1	Ref			Ref			Ref		
2	1.41	0.80–2.49	0.233	1.50	0.63–3.56	0.356	1.57	1.06–2.34	0.025
3	2.16	1.29–3.61	0.003	2.65	1.20–5.85	0.016	2.23	1.55–3.19	<0.001
4	3.00	1.81–4.96	<0.001	3.65	1.66–8.04	0.001	2.66	1.87–3.79	<0.001
Unknown	2.44	1.38–4.34	0.002	2.92	1.22–6.97	0.016	2.04	1.33–3.12	0.001
Treatment group									
Surgery only	Ref			Ref			Ref		
Prior/neoadj, no adj	0.97	0.76–1.24	0.815	0.90	0.66–1.23	0.514	1.16	0.95–1.42	0.141
Adj RT, no prior/neoadj	0.75	0.60–0.94	0.013	0.74	0.55–0.98	0.036	0.67	0.56–0.81	<0.001
Adj RT, w/prior/neoadj	0.62	0.48–0.80	<0.001	0.68	0.50–0.93	0.016	0.69	0.57–0.85	<0.001
Adj CRT, no prior/neoadj	0.79	0.59–1.07	0.133	0.81	0.57–1.16	0.250	0.86	0.67–1.11	0.247
Adj CRT, w/prior/neoadj	0.98	0.72–1.35	0.919	1.14	0.79–1.64	0.499	0.81	0.61–1.09	0.160

TABLE 7 (Continued)

Variables	OS			DSS			RFS		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Other/unknown	0.93	0.68–1.26	0.625	1.06	0.75–1.51	0.729	1.05	0.81–1.34	0.729
Tumor site (epicenter)									
Nasal cavity	Ref			Ref			Ref		
Ethmoid sinus	1.23	1.02–1.49	0.034	1.39	1.10–1.75	0.006	1.01	0.87–1.16	0.933
Maxillary sinus	1.60	1.30–1.97	<0.001	1.86	1.45–2.38	<0.001	1.37	1.16–1.63	<0.001
Skin	1.30	0.94–1.80	0.108	1.16	0.76–1.76	0.487	1.19	0.92–1.54	0.181
Other	1.34	1.07–1.69	0.011	1.49	1.14–1.95	0.003	1.21	1.01–1.45	0.036

Note: Variables not statistically significant were not included in the model, where estimates were blank in the table.

Abbreviations: Adj, adjuvant; CI, confidence interval; CRT, chemoradiotherapy; HR, average hazard ratio estimated from weighted Cox regression; noeadj, neoadjuvant; ref, the reference group; RT, radiotherapy.

techniques,¹² as ethmoid sinus procedures were predominantly carried out through open approaches. In the present investigation, the majority of endoscopic or combined approach procedures were carried out for tumors originating in the ethmoid sinus and nasal cavity. The endoscopic approach offered high negative margin rates as well as lower rates of complications and postoperative mortality. In light of these findings, this transition in the surgical approach for ethmoid tumors leads us to the conclusion that in carefully selected patients, the endoscopic approach is oncologically effective and less morbid than its open counterpart.

Although the overall complication rate has remained identical compared to the previous publication at 31%, there has been a notable decline in postoperative mortality rates from 4.3% to 1.4%. The current study accounts for 45.6% of surgeries as endoscopic or combined/endoscope-assisted procedures. The accumulated experience gained over these 20 years may have contributed to improved patient selection for the appropriate surgical approach, leading to the observed reduction in postoperative mortality. Another plausible factor contributing to the decline in postoperative mortality rates is the nearly doubled use of free flaps compared to the previous report. In our present study, 1379 patients underwent open approach skull base resection with some form of reconstruction, 38% of which ($n = 638$) were free flaps (Table S5). By contrast, the proportion of free flaps in the earlier study was only 21.6%.

It is noteworthy that achieving negative margins in skull base tumor resections remains an arduous task in this area of complex anatomy. The proportion of patients achieving either negative or close margins has persisted at 66%, similar to the previous study's rate of 68.9%. Histologically negative margins are of utmost importance since positive margins are a standalone adverse prognostic factor of OS, DSS, and RFS. Even in

the age of high-quality imaging-based intra-operative navigation systems, it appears that the anatomic constraints of skull base surgery and cancer biology is still hampering our ability to attain negative margins through surgical means.

Perhaps owing to the significant progress in the management of skull base cancer across all disciplines and the increased number of patients receiving adjuvant treatment in our current study, we observed a significant improvement in the 5-year OS, rising from 53.6% in the previous report to 65% in the current cohort. Similarly, DSS has improved from 59.9% to 71.7%, while the 5-year RFS has remained essentially unchanged at 53% in the current cohort compared to 52.8% in the previous study.

These observed improvements in OS and DSS raise the question of whether they might be partially attributed to lead time bias, as the previous cohort encompassed patients treated between 1956 and 2000, whereas the current cohort likely benefited from greater access to in-office endoscopic exams and cross-sectional imaging, leading to earlier cancer diagnoses. Intriguingly, despite the advancements in medical and surgical interventions, the RFS remained unchanged, hinting at tumor biology as a pivotal determinant of patient outcomes.

In conclusion, skull base surgery, which has been extensively revolutionized by endoscopic approaches, remains the cornerstone in managing malignant tumors involving the skull base. Over the past 20 years survival outcomes have improved and postoperative complications and mortality have decreased. Factors which were adverse independent prognostic indicators for OS, DSS, and RFS include older age, comorbidities, histologic type, dural or intracranial tumor involvement, positive margins, advanced pT stage, and maxillary sinus primary site. Adjuvant RT (with or without any prior or neoadjuvant treatment) was associated with improved OS, DSS, and RFS.

AUTHOR CONTRIBUTIONS

Jatin P. Shah: Concept; design; data accrual; analysis; manuscript review. **Helena Levyn:** Data analysis; manuscript preparation; review. **Cristina Valero Mayor:** 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; manuscript review. **Mithat Gonen:** Statistical analysis; manuscript review. **Marc Cohen:** Data contribution; manuscript review. **Snehal Patel:** Project development; data monitoring and transfer; analysis; manuscript preparation and review. **Ian Ganly:** Data contribution; manuscript review. **Prathamesh Pai:** Data contribution and transfer. **Paolo Castelluovo:** 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. **Dan M. Fliss:** 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 Hosai:** 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.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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