ADVANCES IN THE DIAGNOSIS AND TREATMENT OF SKULL BASE TUMORS

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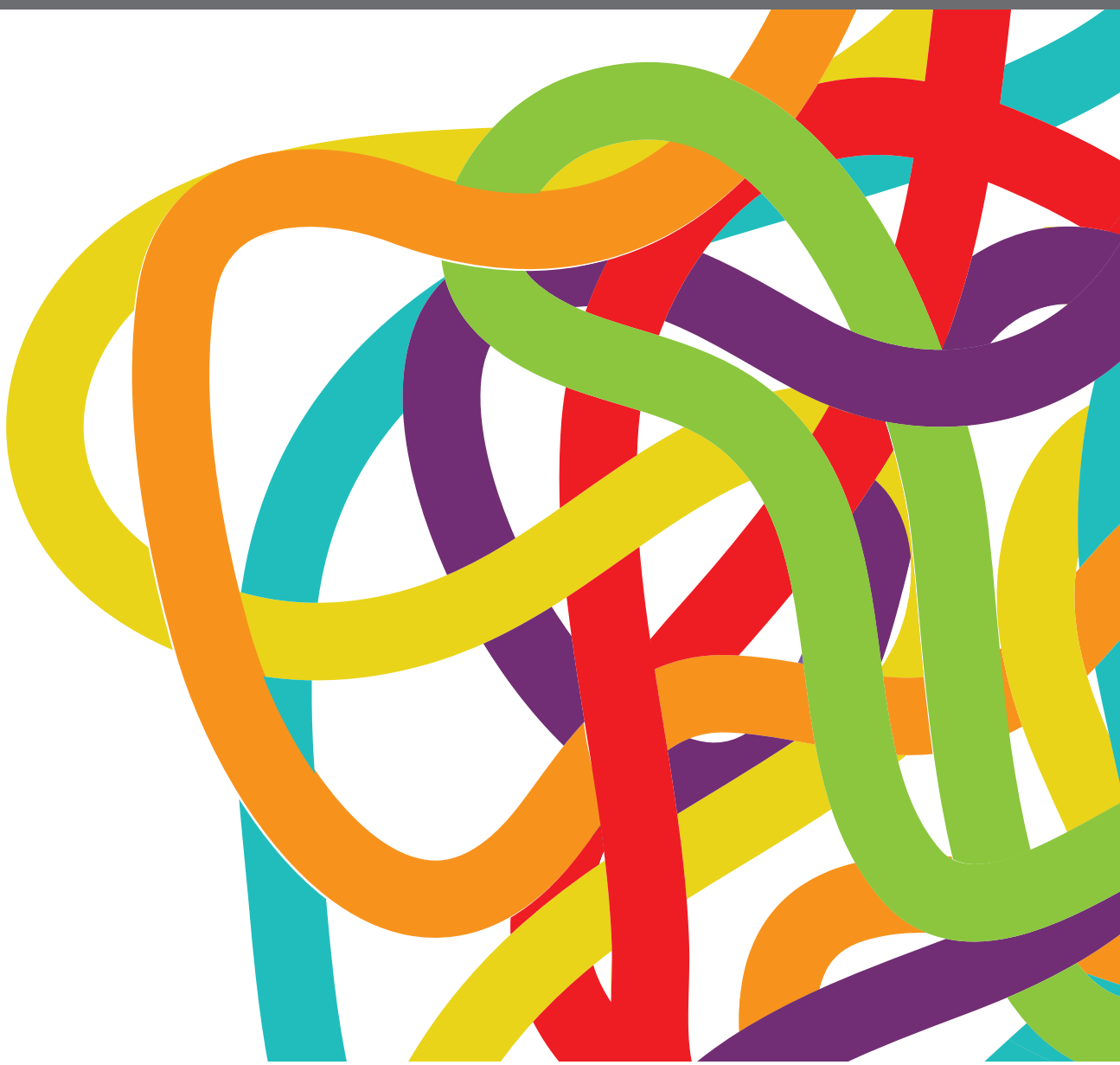

frontiers Research Topics

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ADVANCES IN THE DIAGNOSIS AND TREATMENT OF SKULL BASE TUMORS

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EDITORIAL
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Editorial: Advances in the Diagnosis and Treatment of Skull Base Tumours

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Editorial on the Research Topic

Advances in the Diagnosis and Treatment of Skull Base Tumors

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In this Frontiers Research Topic we sought to highlight some of the most recent advances regarding the diagnosis and treatment of tumours affecting the skull base. The anatomy of the skull base region is complex with numerous critical neurovascular structures in close proximity. Thus, the management of tumours in this region poses a unique challenge for surgeons in order to not only achieve good oncologic outcomes but also to minimize treatment associated morbidity (1, 2). As a result of this anatomical complexity it has been necessary to develop innovative surgical approaches to these tumours. One such advancement in this regard is the introduction of the endoscopic endonasal approach to anterior skull base tumours, in particular for pituitary tumours (3). Van Gerven et al. detailed their initial 10 – year experience with the introduction of this approach within their institution. They retrospectively analysed 369 patients (87.3%; 322/369 pituitary adenomas) with sellar and suprasellar tumours managed in this way. They demonstrated that operative time decreased as surgeon familiarity with the technique increased and favourable outcomes with the endoscopic endonasal approach were observed with a recurrence rate of 20.0% following pituitary adenoma resection. Overall 7.3% (27/369) of their patients suffered a cerebrospinal fluid (CSF) leak postoperatively. CSF leaks are a dreaded complication following endoscopic endonasal resection of anterior skull base tumours and reconstructive approaches to reduce the incidence of this complication were the focus of the review article by Hannan et al. The incidence of CSF leaks following the endoscopic endonasal approach were initially seen as the barrier to the widespread incorporation of this approach into surgical practice (4). The introduction of nasoseptal flap (NSF) as part of a multilayer closure has been effective in reducing the incidence of CSF leak in these cases to below 5% in recent times. Hannan et al. also describe their own 'Dublin

technique' which has resulted in a 1% (1/90) incidence of postoperative CSF leak since its introduction within their institution. They also discuss adjunct methods which may reduce the incidence of postoperative CSF leaks such as the prophylactic use of a lumbar drain. This was the subject of the meta-analysis performed by Guo et al. Their analysis of 8 studies demonstrated that routine lumbar drain use did not significantly reduce the incidence of postoperative CSF leak (OR 0.8; 95% CI 0.37 – 1.74; P=0.57) while routine use of lumbar drain increased the incidence of headache in patients postoperatively.

In tumours affecting the pterygopalatine fossa the maxillary-swing approach (5) is frequently used to access the tumour during surgical resection. However, this approach maintains some inherent limitations such as the close margin at the site of the posterior osteotomy site as well as leaving the surrounding canals and foramina (which may harbour tumour cells) undisturbed. Xie et al. have proposed a novel modification to the classic maxillary-swing approach in order to overcomes some of these limitations. They demonstrated a series of 7 patients with pterygopalatine fossa tumours managed with their modified maxillary-swing approach; achieving en-bloc resection in all 7 cases. One patient (1/7; 14.3%) suffered a locoregional recurrence and no functional morbidity outside of expected facial numbness and epiphora post-operatively was reported.

Despite the major advances in surgical techniques, tumours that affect craniofacial structures still largely require multimodal treatment strategies to achieve local disease control. This was the subject of the review by Konig et al. Their exploration of the literature found that esthenioneuroblastoma and soft tissue sarcomas benefitted from radiotherapy-based adjuvant or neoadjuvant treatment combined with surgery. Sinonasal undifferentiated carcinoma, craniofacial osteosarcoma and neuroendocrine paranasal sinus tumours benefitted from neoadjuvant chemotherapy or adjuvant chemoradiotherapy when combined with surgical resection. On the other hand mucosal melanoma and grade II/III meningiomas appear to be best managed with upfront surgical resection and adjuvant radiotherapy based treatment.

In contrast, radiotherapy-based treatment is utilized as a primary management strategy for nasopharyngeal carcinoma (6). Hua et al. performed an analysis of 1,292 patients with nasopharyngeal carcinoma treated using intensity modulated radiation therapy (IMRT) and concurrent cisplatin. They explored their hypothesis that a prolonged duration of IMRT (IMRT delivered over > 7 weeks) would predispose patients to poor survival outcomes. Patients all received 66 – 70Gy in between 28 – 33 fractions. The prolonged duration of radiotherapy group displayed a significantly worse overall survival (OS) (87.2% v 78.4%; P<0.001) as well as worse distant metastatic free survival, progression free survival and an increased rate of locoregional recurrence. This highlights the necessity of avoiding RT delivery delays in the management of nasopharyngeal carcinoma, a particularly timely finding in the COVID-19 era.

Unfortunately, despite the many advances in the management of skull base tumours many patients still present with advanced disease and an unfavourable prognosis. Komune et al. explored the anatomical factors that impacted survival outcomes in T4 squamous cell carcinoma of the temporal bone. Their retrospective analysis demonstrated that tumour invasion of ossicles, posterior fossa dura or the sigmoid sinus were independent predictors of a reduced 5 year OS. Based with this knowledge they devised a novel 3 factor prognostic classification system for T4 temporal bone squamous cell carcinomas (1. Pterygoid musculature involvement, 2. Ossicular involvement, 3. Posterior fossa dura OR sigmoid sinus involvement). Involvement of an increased number of these structures demonstrated a downward stepwise trend in OS (0 structures involved – 90.9% OS; 1 structure 42.9% OS; 2 structures 25.0% OS; 3 structures – 0.0% OS)

Safi et al. performed a systematic review of the literature to explore the management and outcomes in paediatric patients with esthenioneuroblastoma. Their systematic review of 7 studies and 94 patients suggests that paediatric patients have a tendency to present with advanced disease (69.1%; 65/94 Kadish stage C/D: 20.2%; 19/94 with nodal disease). Paediatric patients also undergo aggressive multimodal therapy with 50% (47/94) of cases receiving triple modality treatment (surgery, radiotherapy and chemotherapy) with the net result of aggressive disease and aggressive therapy being a 5 year OS between 44 – 91% among the included studies.

Finally, this Research Topic was rounded off by a novel lipidomic analysis study by Yu and Wang. They sought to define lipid biomarkers to enable the early diagnosis of laryngeal cancer. Their lipidomic analysis of 29 patients with laryngeal cancer and 36 healthy controls demonstrated that lysophospholipids and phospholipids may serve as potential biomarkers in the early diagnosis of laryngeal cancer.

AUTHOR CONTRIBUTIONS

EFC drafted the original manuscript. All authors listed have revised the text and made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SYSTEMATIC REVIEW
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Efficacy and Safety of Intraoperative Lumbar Drain in Endoscopic Skull Base Tumor Resection: A Meta-Analysis

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Objectives: This study aims to evaluate the efficacy and safety of lumbar drainage (LD) in preventing cerebrospinal fluid (CSF) leaks after endoscopic skull base tumor resection.

Methods: A systematic online search was conducted using PubMed, Embase, Scopus, Web of Science, and Cochrane Library from January 2006 to July 2019. Data analyses were performed by the Cochrane Collaboration's Review Manager 5.3 software.

Results: Eight studies, including two randomized controlled trials and six observational studies, met the inclusion criteria. No significant difference was found in the post-operative CSF leak rate between the LD group and the non-LD group [odds ratio (OR), 0.80; 95%CI, 0.37–1.74; $I^2 = 37\%$; $P = 0.57$). Subgroup analysis of the intraoperative high-flow leaks, including 4 studies and 313 patients, showed that LD was associated with reduced likelihood of post-operative CSF leak (OR, 0.37; 95%CI, 0.17–0.83; $I^2 = 0\%$; $P = 0.02$). The placement of LD was related to increased risk of headache compared with non-LD use, and no significant difference was found in the occurrence of deep vein thromboses and pulmonary emboli between two groups.

Conclusion: LD is not recommended in all patients undergoing endoscopic skull base tumor resection. However, for patients with intraoperative high-flow leaks, LD is effective and safe in reducing risk of CSF leak.

Keywords: cerebrospinal fluid leak, skull base tumor, lumbar drainage, endoscopic endonasal surgery, pituitary

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INTRODUCTION

The endoscopic endonasal approach is a safe and effective surgical technique in the resection of skull base lesions. However, proper skull base reconstruction to prevent the occurrence of post-operative cerebrospinal fluid (CSF) leakage remains a major challenge following these operations (1, 2). The lumbar drainage (LD) is a practice in the management of CSF leaks after endoscopic skull base tumor resection. This device is often kept in place preoperatively or post-operatively to reduce intracranial pressure by continuous drainage, which is believed to facilitate healing of the dural repair under decreased tension and lower the possibility of persistent CSF fistula (3–5). In addition, LD can be conversely used to add saline into the lumbar cistern to provoke descent of skull base tumors, such as pituitary adenomas.

The high-flow leak, which was defined as entrance into an arachnoid cistern or ventricle, is more challenging to deal with (6). Preoperative LD is of particular importance when a high-flow leak is encountered during the procedure. In 2006, the nasoseptal flaps (NSFs) were introduced by Hadad et al. (7). The overall rate of post-operative CSF leak dramatically reduced from 40 to 5% (7, 8). With the increased dependability of the NSFs for skull base reconstructions, some studies reported that LD is being overused in endoscopic skull base surgery when modern reconstructive techniques are used, even when there is a high-flow leak (3, 9). Furthermore, there is little consensus on the use of LD in endoscopic skull base surgery, including identifying suitable patients for LD placement and the duration of LD placement (3, 10). Given the potential side effects including headache, radiculopathy, overdrainage, and decreased patient mobilization, the use of LD has become controversial (11).

Previous studies have investigated the role of LD on the onset of post-operative CSF leaks, but the results have been controversial (10, 12, 13). Therefore, the purpose of our meta-analysis is to explore whether adjunct LD can reduce the rate of post-operative CSF leak in patients undergoing endoscopic skull base surgery and to further find out factors that may contribute to post-operative CSF leaks.

METHODS

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14).

Search Strategy

A comprehensive search strategy included the terms: "lumbar drain," "CSF diversion," "skull base tumor," and "endoscopic endonasal surgery" with appropriate synonyms. PubMed, Embase, Scopus, Web of Science, and Cochrane Library were screened for eligible studies. In light of the substantial advances in techniques and materials with the adoption of the NSFs and other pedicled vascularized tissue flaps used in reconstruction of skull base surgeries, searches were limited from January 2006 to June 2019. We also manually searched the references cited in clinical trial reports or reviews to identify additional relevant studies (**Supplementary Data Sheet 1**).

Eligibility and Exclusion Criteria

We included all research articles published in English that met all of the following criteria: (i) studies should be randomized controlled trials (RCTs) or observational studies; (ii) LD must be placed at the beginning or at the end of the surgical procedure; (iii) LD must maintain into the early post-operative period; (iv) studies were required to use multilayered repair strategy with NSFs for reconstruction; (v) studies must specify that CSF leaks were secondary to endoscopic skull base tumor resection; (vi) studies must contain two arms, LD group and non-LD group; and (vii) studies were required to have reported the number of patients, number of cases with intraoperative LD placement, and the number of cases with post-operative CSF leaks in LD group and non-LD group.

Studies were excluded if they met any of the criteria: (i) studies included patients that underwent open, combined open, and endoscopic or microscopic approaches; (ii) all the articles analyzed about preoperative CSF leaks that resulted from traumatic-, idiopathic-, or surgery-related iatrogenic causes; (iii) studies that did not provide the number of cases with the placement of LD or the number of post-operative CSF leaks in both groups; and (iv) case reports, review articles, editorials clinical guidelines, and unpublished studies (e.g., conference abstracts).

Eligible studies were screened by two independent investigators (XG and YZ). All disagreements were resolved by a third reviewer (YH).

Data Extraction and Outcomes

Relevant data was extracted independently from each study using a standardized form by two investigators (XG and YZ). We extracted the following information from each study: general information (first author's name, year of publication, and location), details of study design, patients' characteristics (including gender, age, BMI), sample size, LD placement protocol, reconstruction strategy, lesions location (anterior fossa, sellar/suprasellar, and posterior fossa), pathological type (i.e., pituitary adenoma), number of cases with intraoperative LD placement, and the number of high-flow intraoperative leaks (when available), number of adverse events (AEs, when available), and post-operative CSF leaks with or without intraoperative LD placement. The primary outcome was the rate of post-operative CSF leak with or without pre- or intraoperative LD placement. Postoperative CSF leaks were determined by clinical evidence of CSF rhinorrhea. The secondary outcome was the rate of AEs that were recorded separately. All disagreements were resolved by a third reviewer (YH).

Risk of Bias Assessment

Two investigators (XG and YZ) independently assessed the risk of bias for the included RCTs using the Cochrane risk of bias tool (15). This tool includes the following domains for methodological evaluation: (i) sequence generation; (ii) allocation concealment; (iii) blinding of participants, personnel, and outcome assessors; (iv) incomplete outcome data; (v) selective outcome reporting; and (vi) other sources of bias. The RCT was ranked as low risk of bias (low risk of bias for all domains), high risk (high risk of bias for one or more domains), or unclear risk (unclear risk of bias for one or more key domains). For observational studies, we used the Newcastle–Ottawa Scale (NOS) (16). The criteria included selection of the exposed/unexposed cohort, comparability of the study group, and the outcome assessment. Studies with a total score of 6 or more were defined as high quality. Publication bias was assessed using a funnel plot. When the shape of the funnel plot was asymmetric, possible publication bias was determined.

Statistical Analysis

Statistical analyses were performed using the Review Manager 5.3 software (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen). The odds ratio (OR) was used to

assess the association between LD use and risk of CSF leak. We performed this meta-analysis under the random-effects model to pool OR with 95% confidence interval (CI) for the incidence of CSF leak. We further analyzed the results in studies classified by several factors (such as the flowrate of intraoperative leak, study design, and pathological type) to explore important clinical differences. The degree of heterogeneity was estimated by I^2. An I^2 value <25% indicated low heterogeneity, a value between 25 and 75% indicated moderate heterogeneity, and a value >75% indicated high heterogeneity. Forest plots were used to graphically display the effect size of each study and the pooled estimates. A $P < 0.05$ was considered statistically significant.

RESULTS

Literature Search and Characteristics of the Included Studies

The search strategy identified a total of 357 studies after removing duplicates. Inclusion and exclusion criteria were applied to

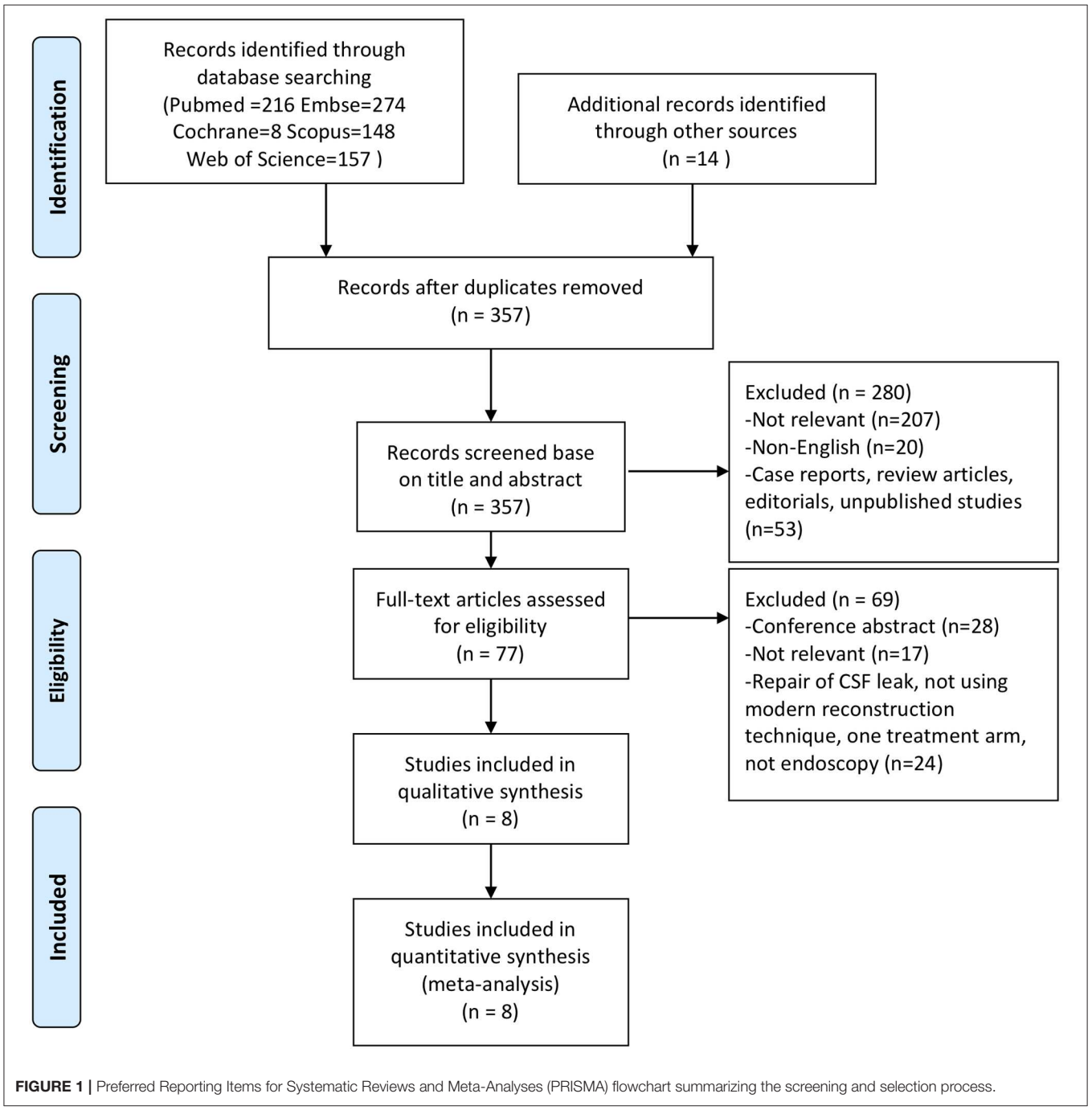

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart summarizing the screening and selection process.

titles and abstracts of 357 articles. This yielded 77 studies that underwent full-text evaluation. Eight studies fulfilled the selection criteria and were included for quantitative analysis, as presented in the flow diagram (**Figure 1**). Demographic characteristics of these eight studies are summarized in **Table 1**. Tumor features and treatment strategies of included studies are summarized in **Table 2**. A total of 1,766 patients were considered suitable for this meta-analysis in these eight studies.

One RCT included in this meta-analysis was judged as low risk of bias, and the other one was judged as high risk of bias according to the Cochrane risk of bias tool. Based on the quality assessment by NOS, all included observational studies were judged as high quality with a score of 7/9 or 6/9 (**Supplementary Table 1**).

Meta-Analysis of Efficacy and Safety

All of the eight studies evaluated the efficacy of LD placement in reducing risk of CSF leak by clinical evidence of CSF rhinorrhea. The overall post-operative CSF leak rate was 4.73% (84 cases). The post-operative leak rate was 5.87% when intraoperative LD was used, and the rate was 4.42% without LD placement. Among the eight studies, no significant difference was found in the post-operative leak rate between the LD group and the non-LD group (OR, 0.80; 95%CI, 0.37–1.74; $I^2 = 37\%$; $P = 0.57$) (**Figure 2**). There were three included studies that reported the AEs of LD (166 patients). The placement of LD was associated with increased risk of headache compared with the non-LD group (OR, 7.22; 95%CI, 1.23–42.29; $P = 0.03$; $I^2 = 0\%$). There was no statistically significant difference in the occurrence of deep vein

TABLE 1 | Demographic characteristics of included studies.

First author, year	Study design	Country	Sample size	Average age	Male (%)	BMI (kg/m^2)	Risk of bias
Patel et al. (6)	Retrospective cohort study	United States	146	NR	NR	NR	High quality*
Garcia-Navarro et al. (17)	Prospective cohort study	United States	46	53.3	NR	NR	High quality*
Ivan et al. (18)	Retrospective cohort study	United States	98	52	43.9%	BMI > 25, 75.5% BMI > 30, 41.8%	High quality*
Pereira et al. (19)	Prospective cohort study	United Kingdom	251	52	54.0%	NR	High quality*
Caggiano et al. (20)	Retrospective cohort study	United States	809	47.2	42.0%	BMI > 30, 32.7%	High quality*
Jonathan et al. (21)	Randomized control trials	India	60	39.2	51.7%	27.9 ± 5.9	High-risk of bias†
Zwagerman et al. (13)	Randomized control trials	United States	170	51.6	38.0%	28.1	Low-risk of bias†
Albarbi et al. (22)	Retrospective cohort study	Saudi Arabia	186	50.3	46.8%	NR	High quality*

**risk of bias was evaluated using The Newcastle–Ottawa Scale (NOS).*
†risk of bias was evaluated using Cochrane risk of bias tool for RCTs.
BMI, body mass index; NR, not reported.

TABLE 2 | Tumor features and treatment strategies of included studies.

First author, year	Pituitary adenoma ratio (%)	Tumor location			Reconstruction strategy	LD placement criteria	LD protocol
		Anterior fossa	Sellar/ suprasellar	Posterior fossa			
Patel et al. (6)	NR	26	114	10	Multilayer reconstruction (NSF)	High-flow leakage	10 ml/h for 3 days
Garcia-Navarro et al. (17)	17.4%	NR	NR	NR	Multilayer reconstruction (NSF, gasket, fat, DuraSeal)	NR	5 ml/h for 1–2 days
Ivan et al. (18)	25.5%	36	24	26	Multilayer reconstruction (NSF, DuraGen, fat, DuraSeal)	NR	10–20 ml/h for 3–5 days
Pereira et al. (19)	75.3%	–	250	–	Multilayer reconstruction (NSF, DuraSeal)	Giant tumor, large suprasellar extension	NR
Caggiano et al. (20)	67.7%	NR	NR	NR	Multilayer reconstruction (NSF, fat graft, fascia lata)	Extended approach	NR
Jonathan et al. (21)	100.0%	–	60	–	Multilayer reconstruction	Randomized	Drain for 5 days
Zwagerman et.al. (13)	11.8%	35	84	50	Multilayer reconstruction (NSF, fascia lata, fat graft)	Randomized	10 ml/h for 3 days
Albarbi et al. (22)	100.0%	–	186	–	Multilayer reconstruction (NSF)	High-flow leakage, intracranial hypertension, poor reconstruction	Drain for 2 days

LD, lumbar drainage; NR, not report; NSF, nasoseptal flaps.

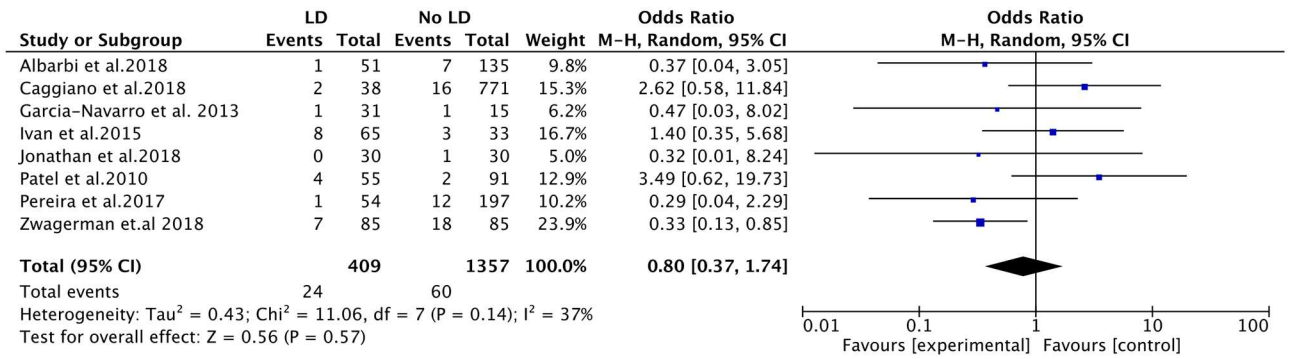

FIGURE 2 | Forest plots showing odds ratio of post-operative cerebrospinal fluid (CSF) leakage in patients after endoscopic endonasal surgeries. CI, confidence interval; LD, lumbar drainage.

TABLE 3 | Subgroup analyses: intraoperative lumbar drainage in endoscopic endonasal skull base surgeries.

Subgroup characteristics	Number of studies	Pooled OR (95% CI)	*P*	Heterogeneity		
				P	I^2	Chi^2
Intraoperative CSF leaks						
• High-flow leaks	4	0.37 (0.17, 0.83)	0.02	0.96	0%	0.31
Prospective vs. retrospective studies						
• Prospective studies	4	0.34 (0.15, 0.74)	0.007	1.00	0%	0.07
• Retrospective studies	4	1.68 (0.73, 3.90)	0.22	0.37	6%	3.18
Tumor type						
• Mixed	3	0.57 (0.21, 1.52)	0.26	0.25	29%	2.81
• Pituitary adenoma	4	0.70 (0.19, 2.54)	0.59	0.21	33%	4.50

OR, odds ratio; CI, confident interval; RCTs, randomized controlled trials.

thromboses and pulmonary emboli (OR, 1.44; 95%CI, 0.53–3.90; $P = 0.48$; $I^2 = 3\%$). In the total of 166 patients, one patient had a retained catheter that was observed without consequence.

Subgroup Analysis

Subgroup analyses were subsequently performed according to the flowrate of intraoperative leak, study design, and pathological type (**Table 3**). Intraoperative LD placement was associated with reduced likelihood of post-operative CSF leak in the setting of high-flow leaks (OR, 0.37; 95%CI, 0.17–0.83; $P = 0.02$; $I^2 = 0\%$; data available from 4 studies, 313 subjects) (**Figure 3**). Regarding the study design, the pooled OR for prospective studies showed a significant association between LD placement and decreased risk of CSF leak (OR, 0.34; 95%CI, 0.15–0.74; $P = 0.007$; $I^2 = 0\%$), whereas no significant difference was found in the retrospective studies (OR, 1.68; 95%CI, 0.73–3.90; $P = 0.22$; $I^2 = 5\%$). According to the ratio of pituitary adenomas, there was no significant difference between the four studies with a ratio of pituitary adenomas >60% (OR, 0.57; 95%CI, 0.21–1.52; $P = 0.26$; $I^2 = 29\%$) and the remaining three studies with a ratio of pituitary adenomas ≤60% (OR, 0.70; 95%CI, 0.19–2.53; $P = 0.59$; $I^2 = 33\%$).

Sensitivity Analysis and Publication Bias

Sensitivity analyses were conducted by excluding one study at a time for each outcome. When we removed the study conducted by Zwagerman et al. (13), the heterogeneity decreased dramatically to 12%.

Publication bias was tested using the data of LD placement and rate of CSF leak ($n = 8$). The shape of funnel plots showed no obvious asymmetry, which indicated the absence of significant heterogeneity between these selected studies (**Figure 4**).

DISCUSSION

This meta-analysis demonstrated that, in patients undergoing endoscopic skull base tumor resection, intraoperative LD placement was not significantly associated with a decreased risk of post-operative CSF leak. As for AEs, the LD placement was related to increased risk of headache, while no significant difference was observed in the occurrence of deep vein thromboses and pulmonary emboli.

These findings are in line with the previous meta-analysis that was based on only three studies (10). To the best of our knowledge, there were some limitations of that meta-analysis. First, the results relied on only three observational studies. Second, the included studies were of relatively poor

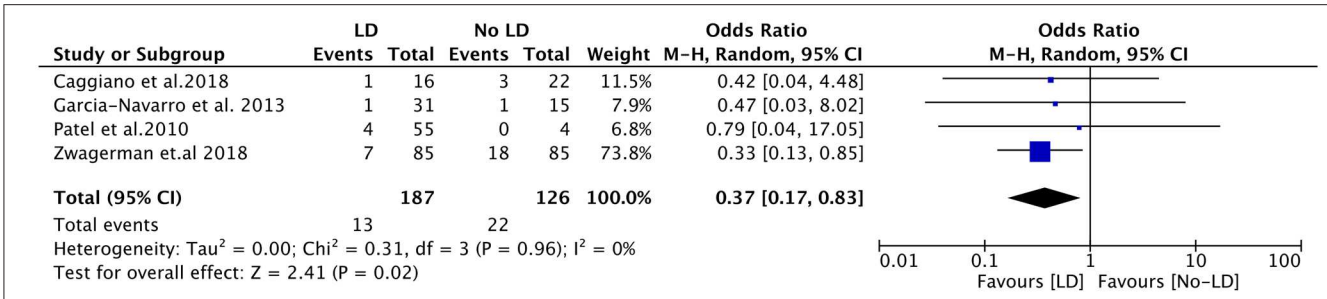

FIGURE 3 | Forest plots showing odds ratio of post-operative cerebrospinal fluid (CSF) leakage in the setting of high-flow leaks. CI, confidence interval; LD, lumbar drainage.

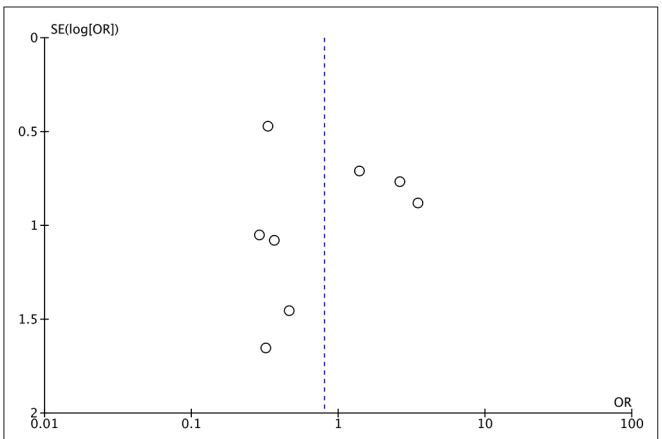

FIGURE 4 | Funnel plots for publication bias. OR, odds ratio; SE, standard error.

quality, which may cause bias and confounding. Third, AEs were not assessed. Our present meta-analysis included recently published studies and examined the efficacy and safety of LD in patients undergoing endoscopic skull base surgery. Subgroup analyses were further performed according to the flowrate of intraoperative leak, study design, and pathological type.

Placement of intraoperative LD is often used for the purpose of providing a controlled, low-resistance egress of CSF during initial healing. To date, numerous studies have described various techniques to reduce the rate of post-operative CSF leak, including the use of multilayer closures with synthetic and autologous materials, the NSFs, the gasket seal, and Foley balloon (17, 23–25). Some studies reported that LD may not be needed in the endoscopic skull base tumor resection (3, 9). Tien et al. (26) published a systematic review on the management of post-operative CSF leaks in which they concluded that LD did not significantly contribute to successful repair in most low- or high-flow leaks. However, by analyzing the results, it is unusual that the CSF leak rate was higher in patients with LD placement than those without. This might represent a patient selection that LD was more likely to be used in higher-risk cases. Some studies also suggested that LD was not necessary in all high-flow CSF leaks (26–28). They reported 90–100% success rate from endoscopic repair without post-operative CSF diversion (24, 27).

In the recent RCT conducted by Zwagerman et al. (13) high-flow patients were recruited and randomized to either LD or no drainage. They found that LD placement was associated with decreased risk of post-operative CSF leak. The CSF leak rate was, respectively, 8.2% in the LD group and 21.2% in the non-LD group. Eloy et al. (27) reported a higher success rate from endoscopic repair without LD placement, possibly because they defined high-flow leak as a "leak brisk enough to visualize egress of CSF without Valsalva". However, generally, most clinicians agreed with the definition, "entering into an arachnoid cistern or ventricle" (6, 13, 17, 29). To investigate the relationship between intraoperative high-flow leaks and LD use, we extracted data from four studies that specified the flowrate of intraoperative leak and performed the subgroup analysis. The result indicated that there was a statistically significant difference between LD group (7.0%) and non-LD group (17.5%). Furthermore, another RCT conducted by Lavigne et al. (30) enrolled patients with high-flow leaks of the anterior or post-erior cranial fossa. Their conclusion further supported our findings. However, this study has been only published as a meeting abstract without detailed data.

A discrepancy was identified in some studies that included pituitary lesions in the same category as large skull base lesions, such as meningiomas and craniopharyngiomas. Most pituitary tumors are located in the sellar region without an arachnoid extension and should be analyzed as a separate category, despite some pituitary adenomas are large enough and their removal can result in high-flow CSF leaks. The subgroup analysis based on the ratio of pituitary adenoma was performed, indicating that CSF leaks were not associated with the pathological type of pituitary adenoma.

Reported complications of the LD include headache, nerve root irritation, meningitis, tension pneumocephalus, acute or delayed intracranial hypotension, and subdural hemorrhage (3, 11). In our analysis, although serious complications were not observed in the total 166 patients, the risk of post-operative headache increased when the LD was placed (**Table 4**). In addition, there was one patient who suffered from a retained catheter without consequence, and it indicated that LD placement was associated with potential risk of reoperation. Some studies reported that LD placement was associated with an additional 2.0–3.2 days in the hospital (20, 22). Indeed, LD

TABLE 4 | Pooled ORs of adverse events.

Adverse events	Including study number	Pooled OR (95% CI)	*P*	I^2
Headache	3	7.22 (1.23, 42.29)	0.03	0%
DVT and PE	2	1.44 (0.53, 3.90)	0.48	3%
Retained catheter	1	3.04 (0.12, 75.57)	0.50	NA

OR, odds ratio; DVT, deep vein thromboses; PE, pulmonary emboli.

was left in place only for 1–3 days in most of our included studies (**Table 2**). Another aspect was that LD placement was associated with aforementioned patient selection (giant tumor, large suprasellar extension, and poor reconstruction). This may be a potential confounding factor affecting the length of stay. As for meningitis, several studies indicated no significant association between LD placement and post-operative infection or meningitis (5, 13, 21). In conclusion, the risks of LD placement should not be dismissed, and for those carefully selected, high-flow leak patients, the benefits of LD outweigh the risks.

Several limitations in this meta-analysis should be addressed. First, despite of rigorous eligibility criteria and a comprehensive search, the majority of included studies in this meta-analysis are observational studies that have inherent selection bias and confounders. In terms of generalizability due to larger and wider-spread samples, observational studies might be of value to explain the relationship between the LD placement and CSF leakage. Second, the RCT conducted by Jonathan et al. was judged as a high bias risk due to lack of blinding of the surgeons (21). High risk of bias may weaken confidence in the results. However, it was well-designed and met our inclusion criteria. Besides, only one in six domains met the criteria of high risk of bias. To make the result more convincing, we should include more studies with low risk of bias in the future. Third, a moderate degree of heterogeneity may limit our findings. On this point, we conducted the sensitivity analysis using the leave-one-out method. Heterogeneity decreased significantly from 37 to 12% after omitting studies conducted by Zwagerman et al. (13). Most included studies were observational studies, and only two of them were RCTs in our meta-analysis. As we know, RCTs have more strict study design and inclusion criteria than observational studies. The RCT conducted by Zwagerman et al. (13) only recruited patients with high-flow leaks; maybe this was the source of heterogeneity. Although the heterogeneity decreased the RCT conducted by Zwagerman et al. (13) was when removed, the heterogeneity (37%) of including all studies was also acceptable. Hence, this study should be included. Finally, subgroup analyses of the materials used in repair was not conducted due to limited data. This may be another confounder for this analysis. More studies with detailed evidence are needed to confirm the relationship.

This meta-analysis provides the up-to-date evidence, which has implications for clinical decision-making. This finding supports the importance of LD placement in the setting of high-flow leaks for the prevention of post-operative CSF leaks after endoscopic skull base tumor resection. Neurosurgeons should assess the benefits of LD placement and set these against the risks.

CONCLUSION

Our meta-analysis provides evidence for efficacy and safety of intraoperative LD placement in preventing CSF leaks after endonasal skull base tumor resection and reconstruction. In the setting of intraoperative high-flow leaks, LD decreases the incident rate of CSF leak. Based on current evidence, LD is not recommended in all patients undergoing endoscopic skull base tumor resection.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

XG and YH: development of methodology. XG and YZ: acquisition of data, analysis, and interpretation of data. XG: writing of the original manuscript. YH: revision of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.00606/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Treatment Strategies and Outcomes of Pediatric Esthesioneuroblastoma: A Systematic Review

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Introduction: Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a small round blue cell tumor of nasal neuroepithelium first described in 1924. Though this tumor is especially rare in the pediatric population with an incidence of <0.1 per 100,000, it is the most common pediatric nasal cavity neoplasm. The purpose of this systematic review is to examine the treatment modalities utilized for pediatric esthesioneuroblastoma and overall survival.

Methods: A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Pubmed, EMBASE, and Ovid MEDLINE databases were queried for studies pertinent to treatment modalities for pediatric esthesioneuroblatoma and survival outcomes.

Results: Two hundred and seventy-sixth articles were identified, with seven meeting inclusion criteria. Ninety-four patients with an age range of 0.9–21 years old with esthesioneuroblastoma were included. Nearly 90% of patients were of stage Kadish B or C at time of presentation, while 20% presented with cervical lymphadenopathy. Only about 10% of patients underwent single modality therapy. Overall, 5-year survival ranged from 44 to 91% with a median follow-up of 3–13 years.

Conclusion: Children with esthesioneuroblastoma usually present at an advanced stage and undergo multi-modality therapy at a higher rate than adult patients. There is a wide range of documented overall survival though this lack of precision could be due to a paucity of patients.

Keywords: esthesioneuroblastoma, olfactory neuroblastoma, pediatric skull base surgery, endoscopic skull base surgery, skull base tumor, pediatric neuroendoscopic surgery, head and neck cancer, skull base cancer

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INTRODUCTION

Esthesioneuroblastoma, also known as olfactory neuroblastoma, is a small round blue cell tumor of nasal neuroepithelium first described in 1924 (1). This tumor comprises about 28% of pediatric nasal cavity cancers and is the most common nasal cavity neoplasm in children (2). Presenting symptoms usually include nasal obstruction, facial pain, epistaxis, and visual and intracranial complications based on extent of tumor spread (3, 4). Computed tomography (CT) and magnetic

resonance imaging (MRI) play a complimentary role in diagnosis, as CT provides information on osseous erosion while MRI provides insight into soft tissue spread (5). Adult patients are usually treated with surgical resection followed by postoperative radiation therapy (6). However, due to the rarity of this diagnosis in children, there is limited literature analyzing treatment algorithms. Thus, the purpose of this study is to examine the treatment modalities used for pediatric esthesioneuroblastoma and the overall survival of these patients.

METHODS

A comprehensive review of the English language-literature was performed from the PubMed, EMBASE, and Ovid MEDLINE databases through the OVID portal. The search was conducted using the phrase "pediatric esthesioneuroblastoma." Inclusion criteria were defined using the Population, Intervention, Control, Outcome, and Study Design (PICOS; **Table 1**) approach (7). Studies included in the review were those with pediatric patients with a diagnosis of esthesioneuroblastoma and with documented survival data after undergoing treatment. Case series with fewer than five patients were excluded. A systematic search of the literature was performed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) literature selection process (8).

Two reviewers (C.S. and D.S.) independently examined all articles in a standardized manner to determine study eligibility and then compared highlighted articles. All duplicate records were removed. The abstract of every citation was screened for relevance to pediatric esthesioneuroblastoma. Case reports and irrelevant articles were discarded. Full text articles were then assessed for eligibility. Clinical studies with fewer than five patients and those without discussion of either treatment modality or overall survival were excluded. Furthermore, only manuscripts evaluating pediatric esthesioneuroblastoma exclusively were included to prevent ambiguity of data from series that included both pediatric and adult patients. The remaining articles meeting all inclusion and exclusion criteria were included for qualitative and quantitative analysis.

Data collected from each study included authors, year of publication, study design, patient demographics, patient population, number of patients, and treatment modalities used. Outcome measures examined included overall survival. A meta-analysis could not be performed due to the heterogeneity in reporting of treatment modalities and outcome measures.

TABLE 1 | Population, Intervention, Control, Outcome, Study Design (PICOS) Inclusion Criteria.

Population	Inclusion criteria	Exclusion criteria
	Pediatric	**Adults**
Intervention	1. Treatment of esthesioneuroblastoma including surgical excision, chemotherapy, and/or radiation therapy	1. No mention of treatment modality
Comparator	1. Evaluate the most commonly used treatment modalities for pediatric esthesioneuroblastoma	
Outcome	1. Disease free and overall survival for pediatric esthesioneuroblastoma	
Study design	Case series, retrospective, prospective	Case series with <5 patients, case reports

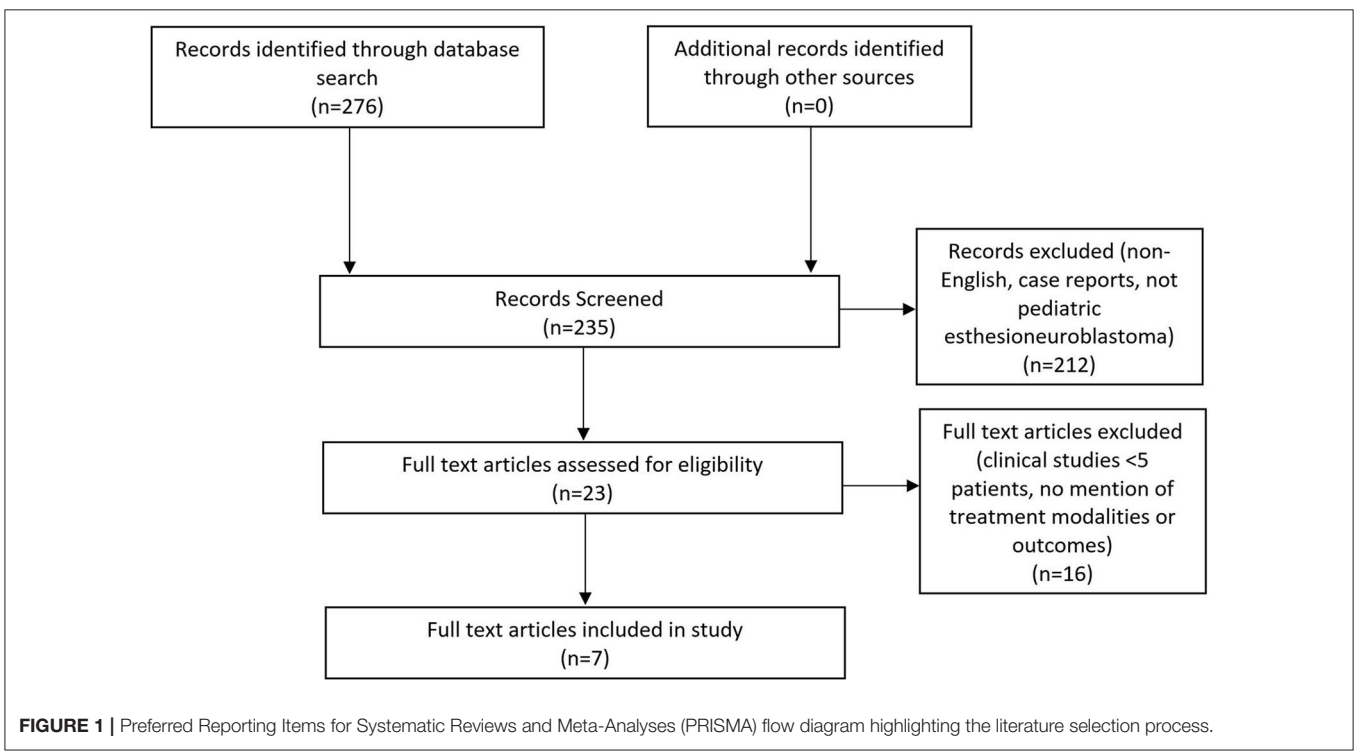

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram highlighting the literature selection process.

TABLE 2 | Pediatric esthesioneuroblastoma treatment modalities and survival outcomes.

Author, year	Timeline	Number of patients	Median age, yr (range)	M:F	Kadish stage	% with cervical LN metastases	Treatment	Median follow-Up, yr (range)	Survival
Bisogno et al. 2012 (9)	1980–2008	9	9.9 (0.9–18)	6:3	B–3	22.2% (2/9)	Chemo/RT–3 Chemo/Surg–1 Triple Mod–5	13.4 (9.2–22.9)	PFS–77.8% (33.6–93.9%) OS–88.9% (43.3–98.4%)
Dumont et al. 2020 (10)	1990–2005	18	12.2 (0.9–18)	10:8	A–1 B–3 C–10 D–4	10.5% (2/19)	Surg/RT–4 Chemo–4 Chemo/RT–2 Chemo/Surg–3 Triple Mod–5	7.6 (3.8–17.9)	PFS = OS–44.4% (± 11.7%)
Eich et al. 2005 (3)	1979–2001	19	14 (5–20)	9:10	B–4 C–15	11.1% (2/18)	Surg–4 Surg/RT–1 Chemo/RT–2 Triple Mod–12	3.1 (0.25–23)	PFS–55% ± 13% OS–73% ± 12%
Kababri et al. 2014 (4)	1982–2002	11	14 (0.8–18)	3:8	B–5 C–6	9.1% (1/11)	Surg/RT–1 Chemo/RT–1 Chemo/Surg–1 Triple Mod–8	8.8 (3.8–16.4)	PFS = OS–91% (62–98%)
Kumar et al. 2002 (11)	1989–2000	5	13 (5–16)	4:1	A–1 B–1 C–3	20% (1/5)	Chemo/RT–2 Chemo–1 Chemo/Surg–1 Triple Mod–1	N/A	3/5 dead at 18 months after diagnosis
Lucas et al. 2015 (12)	2000–2013	8	10 (4–21)	2:6	B–3 C–1 D–4	37.5% (3/8)	Surg/RT–2 Chemo/RT–2 Triple Mod–4	4.6 (4–21)	OS–87.5%
Venkatramani et al. 2016 (13)	1990–2014	24	12 (0.6–20)	6:18	B–8 C–16	33.3% (8/24)	Surg–1 Surg/RT–10 Chemo/RT–1 Triple Mod–12	3.8 (0.5–21.9)	PFS–73.7% (50.5–87.3%) OS–72.8% (46–87.9%)

M, Male; F, Female; LN, lymph node; Chemo, chemotherapy; RT, radiation therapy; Surg, surgery; Triple Mod, Triple Modality Therapy; PFS, Progression Free Survival; OS, Overall Survival.

RESULTS

The initial database query identified 276 articles (**Figure 1**). After the duplicates were removed, the abstracts of the remaining 235 citations were screened for articles related to pediatric esthesioneuroblastoma that were not case reports. The remaining 23 articles from this initial screen underwent a full-text assessment for eligibility. Manuscripts that did not specify treatment modalities or lacked data on survival outcomes were excluded.

A total of seven articles met final inclusion criteria. A summary of these articles is found in **Table 2**. A total of 94 pediatric patients with an age range of 0.9–21 years and a male to female ratio of 43–57% were included in this study. All studies were retrospective case series and included patients treated between 1980 and 2014. There was a lack of uniformity amongst the articles in reporting how patients were diagnosed with esthesioneuroblastoma. Some simply described that the diagnosis was confirmed histologically while others were more detailed and explained that biopsy showed sheets and nests of round blue cells with scant cytoplasm. Some authors even described that immunohistochemistry of presumed masses stained positive for chromogranin, synaptophysin, and neuron-specific enolase. Studies did not uniformly comment on Hyam's histological grading. CT and MRI were used to determine the extent of spread of the mass and provide Kadish staging. 2.1% (2/94) of patients were Kadish A, 28.7% (27/94) were Kadish B, 60.6% (57/94) were Kadish C, and 8.5% (8/94) were Kadish D as seen in **Table 3**. Cervical lymph node metastases were found in 20.2% (19/94) of patients.

TABLE 3 | Kadish stage upon diagnosis.

Kadish Stage	# of patients (%)
A	2/94 (2.1%)
B	27/94 (28.7%)
C	57/94 (60.6%)
D	8/94 (8.5%)

Kadish Staging: A – tumor confined to nasal cavity; B – involvement of one or more paranasal sinuses; C – extension beyond the paranasal sinuses involving cribiform plate, skull base, or orbit; D – regional lymph node or distant metastasis.

Each study was evaluated for the therapeutic modalities used to treat pediatric esthesioneuroblastoma including neoadjuvant and adjuvant chemotherapy (CT), radiation therapy (RT), and surgical resection, as seen in **Table 4**. For chemotherapy, authors described most commonly using a combination of

TABLE 4 | Treatment modalities.

Treatment Modality	# of patients (%) *N* = 94 patients
Surgery	5 (5.3%)
Chemo	5 (5.3%)
Chemo + RT	13 (13.8%)
Surgery + RT	18 (19.1%)
Surgery + Chemo	6 (6.4%)
Triple Modality Therapy	47 (50%)

Chemo, chemotherapy; RT, radiation therapy.

agents including but not limited to vincristine, doxorubicin, cyclophosphamide, cisplatin, etoposide, and isofosfamide. These therapies were adapted from the chemotherapy protocols set in place at each institution and/or country for pathologies such as rhabdomyosarcoma, neuroblastoma, and Ewing's sarcoma. While authors were not specific about exact protocol used, one did mention that treatment would vary from five to 15 cycles. Chemotherapy was utilized in 75.5% of patients (71/94). Overall, radiation therapy was utilized in 83.0% of cases (78/94) and varied between proton therapy as well as more traditional photon radiotherapy. Most articles described using a median radiation dose of 50–60 Gray (Gy) with ∼2 Gy per fraction for a median number of fractions ranging from 25 to 32. Only one study described using proton therapy while another specifically stated that linear accelerators were used to form anterior and wedged lateral radiation fields for the treatment field. Surgical resection was performed in 80.9% of cases (76/94) and involved endoscopic endonasal resection or craniofacial resection with or without craniotomy, as well as cervical lymphadenectomy when indicated.

Single modality therapy was utilized in 10.6% of patients (5 surgery, 5 CT). Dual modality therapy was used in 39.4% of patients (18 surgery and RT, 13 CT and RT, 6 CT and surgery). Triple modality therapy was used in 50% (47/94) of patients. Both the progression free survival and overall survival ranged from 44.4 to 91% with median follow-up of 6.1 years. Five of the seven included studies have an overall survival >70% indicating an overall positive prognosis. Unfortunately, due to the heterogeneity of the reported data as well as varying treatment modalities utilized, a meta-analysis could not be performed.

DISCUSSION

Pediatric esthesioneuroblastoma is a very uncommon pathologic diagnosis. As a result, no single center or provider has significant treatment experience. Our aim in this systematic review was to synthesize the available literature to determine commonly used treatment modalities as well as overall survival.

Regarding patient presentation, only 2.1% of pediatric patients presented with a Kadish stage A tumor limited to the nasal cavity. In contrast, a study looking at over 800 patients from the National Cancer Database found that almost 22% of adults were diagnosed with a Kadish stage A tumor, possibly indicating that children present with a more aggressive phenotype of the disease (9). This is further supported by the fact that adult patients were found to have regional metastases to the cervical lymph nodes in 7.3% of patients while children and adolescents were found to have a 20.2% regional metastasis rate in our study. These data reinforce the concept that esthesioneuroblastoma in the pediatric population is a more aggressive tumor compared to adult disease. This finding emphasizes the importance of a unique treatment paradigm in managing pediatric esthesioneuroblastoma.

Treatment strategies differ significantly between pediatric and adult patients. Adult patients usually undergo surgical resection, radiation therapy, or a combination of both (3, 4, 12, 14). However, our study found that 50% of patients underwent triple modality therapy with surgical resection, CT, and RT, while only about 10% of patients underwent single modality therapy. Surprisingly, nearly half of adult patients in a large series underwent single modality therapy while extensive surgical excision, CT, and RT was reserved for <15% of patients (14). Furthermore, in another study involving 22 patients with esthesioneuroblastoma with a median age of 45, all patients underwent craniofacial resection as well as radiotherapy for treatment. Thirty-six percentage of patients underwent combination proton and photon radiotherapy while the rest underwent proton therapy. In this group, only 22.7% of patients were treated with chemotherapy such as etoposide, cisplatin, and carboplatin. These data further suggest the treatment dichotomy between adults and pediatric patients with esthesioneuroblastoma (15). Apart from a higher stage tumor requiring more aggressive therapy, these discrepancies in treatment modalities could also be related to the consideration of post-treatment sequelae for children. For example, young children have small nasal cavities making oncologic surgical resection challenging with vital structures such as the orbit and brain in such close proximity (13). Furthermore, radiation therapy of the head and neck in young children requires special consideration due to the potential for endocrine dysfunction and an increased risk of secondary malignancy later in life (13).

Regarding survival outcomes, we found an overall 5-year survival ranging from 44 to 91% with several years of follow-up in most studies. This finding is similar to several studies involving adult patients that demonstrate an overall 5-year survival ranging from about 60 to 95% (14–16). This wide range in overall survival could be explained by the relatively small number of patients involved in each study with a variety of treatment strategies, making the task of identifying an optimal treatment strategy even more challenging. A major limitation in this study is that all of the included publications were small retrospective case series. Each author used individualized treatment algorithms and varied outcome measures that prevent qualitative analysis. Furthermore, not every study commented on survival with respect to unique treatment modalities, so definitive conclusions about which treatment strategies were more beneficial could not be made. Due to the rarity of pediatric esthesioneuroblastoma, continuing to gather high volume data from several different institutions will be key in determining the optimal treatment strategy with the best outcome.

CONCLUSION

Esthesioneuroblastoma is a rare small round blue cell tumor found in the nasal cavity and paranasal sinuses. Children appear to present with a more locally and regionally advanced tumor when compared to adults, likely predisposing providers to use more multimodality therapy. Moreover, it is possible that due to the long term sequelae of radiation therapy and extensive surgical resection, triple modality therapy is favored to provide a more balanced approach in treating the cancer and limiting complications. The overall 5-year survival in pediatric patients is varied and future studies are needed in order to determine the ideal treatment regimen that will limit lifelong morbidity in this young patient population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept development, data analysis, and manuscript composition and editing.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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The Role of Adjuvant Treatment in Craniofacial Malignancy: A Critical Review

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Background: Tumors originating from the craniofacial region usually present in a locally advanced stage with frequent involvement of adjacent sites and have a strong tendency for local recurrence in the absence of adjuvant therapy, even when the original surgical resection was presumed to be radical. In the past decades, several advances in the radiological diagnosis and treatment of craniofacial malignancies have been introduced. There are, however, no randomized trials that define the optimal multimodal treatment of these tumors because of their rarity as well as heterogeneity in both histology and site of origin. The aim of this study was to conduct a critical review of the role of adjuvant therapy in the treatment of craniofacial malignancy.

Method: We conducted a critical review of the past and contemporary literature available, focusing on adjuvant oncological treatments of the most common craniofacial malignancies.

Results: Preoperative radiotherapy can have a documented role in the treatment of olfactory neuroblastoma and soft tissue sarcoma, while preoperative chemotherapy can be advocated in the treatment of sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, olfactory neuroblastoma, and craniofacial sarcoma (both soft-tissue and high-grade osteosarcoma). Postoperative radiotherapy has a well-established role in the treatment of most craniofacial malignancies. The role of postoperative chemotherapy is unclear in most histologies, but is commonly used during the treatment of well-selected cases of paranasal sinus carcinoma, olfactory neuroblastoma, mucosal melanoma, soft tissue sarcoma and high-grade craniofacial osteosarcoma.

Discussion: Alongside developments in surgery, there have also been improvements in diagnostics, radiotherapy, and chemotherapy. Implementation of novel radiation techniques allows delivery of higher radiation doses while minimizing irradiation-related morbidity. Better understanding of tumor biology allows the construction of more

complex treatment strategies, incorporating adjuvant chemotherapy either pre- or postoperatively. In the era of personalized targeted therapy, rapid strides are being made to identify specific tumor-targets for use of novel biologic agents, with the potential to change current management paradigms.

Keywords: skull base malignancies, adjuvant therapies, sinonasal cancer, olfactory, neuroblastoma, mucosal melanoma, malignant meningioma, soft tissue sarcoma

INTRODUCTION

The craniofacial region consists of several complex anatomic areas, closely related to the skull base, which pose surgical challenges for neurosurgeons and otorhinolaryngologists alike. Tumors originating from this region usually present in a locally advanced stage at diagnosis due to innocuous presenting symptoms and with frequent involvement of adjacent sites. In addition, there is a strong tendency for local recurrence in the absence of adjuvant therapy, even when the original surgical resection was presumed to be radical.

In the past decades, several advances in the radiological diagnosis and treatment of craniofacial malignancies have been introduced. Surgery in these locations may have dramatic functional and life-threatening consequences that sometimes prohibit radical surgical resections. However, novel surgical procedures and adjuvant modalities have made treatment feasible for malignancies previously considered impossible (1). There are no randomized trials that define the optimal multimodal treatment of malignancies of the craniofacial region because of the rarity of these tumors as well as their heterogeneity in both histology and site of origin.

This study aims to provide a critical review of the role of adjuvant therapy in the treatment of craniofacial malignancy.

Craniofacial Malignancies

The term "craniofacial" refers to the parts of the head enclosing the brain and the face from the upper part of the maxilla, largely corresponding to the *suprastructure*. This anatomical region is affected by a variety of tumors with clinical, etiological, pathological, and genetic features distinct from other tumors in the head and neck. The skull base forms the floor of the cranial cavity and separates the brain from other facial structures. It can be subdivided into three regions: the anterior, middle, and posterior cranial fossae. The most important anatomic structure above the sinonasal region is the anterior skull base. This part of the skull base is aberrant to other regions of the cranial skeleton as it displays a unique configuration of an osseous cranial vault with depressions, ridges, and septa. The anterior skull base stretches between the posterior wall of the frontal sinus anteriorly, to the roof of the sphenoid sinus marked by the anterior clinoid processes and the planum sphenoidale, posteriorly. The lateral boundaries are formed by the frontal bone. The anatomical connection between the midface and neurocranium is formed by the maxilla, the nasoethmoidal complex, the palatal and vomerine bone, and the pterygoid process of the sphenoid. The jaw is constituted by two main parts: the maxilla (upper part) and the mandibula (lower part).

Although these tumors may have similar anatomical locations, they can have considerably different characteristics and clinical behavior. In addition, there is no universally accepted grading and staging system available for these tumors.

Malignancies in this region are rare and encompass a variety of cancers arising from different sites. While emphasizing their rarity, the most common and representative of these malignancies are sinonasal carcinoma, olfactory neuroblastoma, mucosal melanoma, soft-tissue sarcoma, malignant meningioma and malignant tumors of the bone and cartilage, such as osteosarcoma, chondrosarcoma, and chordoma.

ADJUVANT THERAPIES

Adjuvant therapies might be indicated when their efficacy—alone or in combination—is greater than their cumulative toxicity, depending on both patient-related and treatment-related factors (**Table 1**). They are usually administered with the intent of improving loco-regional control (i.e., enhancing the effect of surgery) with an impact on overall survival. Most commonly, these therapies include radiotherapy and/or chemotherapy administered pre and/or postoperatively (neoadjuvant and adjuvant therapy, respectively). In addition, novel therapies are currently being investigated, including agents selectively targeting extra- and intracellular signaling pathways, i.e., immune, hormone- and targeted therapies. At present, however, these therapies are mostly limited to therapy for overt metastatic disease (i.e., not as an adjuvant therapy), without primary surgical treatment.

Adjuvant therapies can be administered as a local or systemic treatment against the tumor (primary or recurrent), the resection site, local or regional lymph nodes, or to combat assumed distant subclinical/micrometastases.

Radiotherapy is used to achieve disease control at the tumor or lymph node site, and can be delivered using either using photons (X-rays) or heavy particles (proton beams or carbon ions). Fractionation is a commonly used process during the treatment of craniofacial malignancies, allowing maximal tumor cell death and minimal damage of nearby organs at risk (e.g., cranial nerves, eyes, brain).

When used as an adjuvant treatment, chemotherapy can be given as a radiosensitizer (i.e., rendering tumor cells more sensitive to radiation therapy by counteracting the radio-protective effect of tumor hypoxia). The two most commonly used agents are the cytotoxic agent cisplatin and the hypoxic modifier nimorazole.

TABLE 1 | Factors influencing the efficacy of adjuvant therapies.

Patient/tumor-related	Treatment-related
Tumor histology, grade and stage	Treatment dose
Tumor oxygenation	Extent of body area treated
Mitotic fraction	Method of delivery
Genetic factors	Timing of delivery
Patient comorbidities	Combination of treatment
Medications and allergies	Pervious treatments
Age and performance status	Cumulative toxicity

TABLE 2 | Factors influencing the toxicity of adjuvant therapies.

Patient-related	Treatment-related	Tumor-related	Physician-related
Performance status	Ports used	Tumor site	Competence
Nutrition status	Energy selection	Tumor stage	Convenience
Hydration status	Dose	Tumor grade	Cost
Skin care	Beam modifying	Nodal status	Facilities
Oral hygiene	Fractionation		Multidisciplinary
Dental hygiene	Setup errors		
	Quality assurance		

However, chemotherapy can also be given as induction therapy or to minimize the subsequent risk of developing distant metastasis. For craniofacial malignancies, chemotherapy is usually administered as a part of a standardized regimen, and often as part of study protocols. The dosage is challenging; too low a dosage might be ineffective against the tumor, whereas too high dosage can lead to excessive—and sometimes intolerable—toxicity. All chemotherapy regimens require that the recipient is actually capable of undergoing treatment.

Targeted therapy interferes with specific molecules needed for carcinogenesis and tumor growth by targeting and blocking extracellular signals, rather than by blocking intracellular signals and interfering with all rapidly dividing cells (as traditional chemotherapy does) (2). A variety of molecular targets may be therapeutically relevant in some malignancies of the craniofacial region. In addition, identification of specific tumor markers may provide prognostic information that can be used to guide decision making and the selection of additional therapy. In some cases, participation in clinical trials that investigate immunotherapy and other novel approaches may be considered for patients with residual, recurrent, or metastatic disease (3–12).

Toxicity in Oncological Treatment

Toxicity is influenced by patient-, treatment-, tumor- and physician-related factors (**Table 2**). Toxicity can also be treatment specific (**Table 3**). Radiation therapy may lead to several local and site-specific complications in the craniofacial region affecting the skin of the head, the eyes, and the brain. Such complications include epithelial surface damage, swelling, fibrosis, dryness, and cognitive decline. Chemotherapy, on the other hand, may lead to systemic complications such as immunosuppression, myelosuppression, gastrointestinal distress, organ damage, and fatigue. Both radiation therapy and chemotherapy may cause nausea and vomiting, hair loss, ototoxicity and neuropathy. In addition, secondary neoplasm is a possible long-term complication of both modalities. Toxicities might be cumulative through life, and the administration of adequate doses of adjuvant therapies might not be possible for the treatment of a secondary neoplasm, or—in the worst case—the therapy might not be available at all.

TABLE 3 | Treatment-specific toxicities.

Radiotherapy	Chemotherapy
Nausea and vomiting	Immune and myelosuppression
Epithelial surface damage	Gastrointestinal distress
Local swelling and fibrosis	Organ damage
Reduced wound healing	Fatigue, nausea, and vomiting
Hair loss	Neuropathy
Neuropathy and cognitive decline	Hair loss
Secondary neoplasm	Secondary neoplasm

TABLE 4 | Potential benefits of adjuvant therapies pre and postoperatively.

Preoperative therapy (neoadjuvant)	Postoperative therapy (adjuvant)
Size reduction of primary tumor	Eradication of micro and macroscopic tumor rest
Eradication of micrometastatic disease	Reduced risk of recurrence and metastases

Timing of Adjuvant Therapies

Adjuvant therapy administered preoperatively (neoadjuvant) may shrink the primary tumor at the same time as instituting a treatment to avoid lymph node and/or visceral micrometastases developing into over metastases. Tumors with a low mitotic fraction experience a weaker response to radiation; in such cases, tumor control is often defined as lack of growth (and/or reduced cell density) rather than diminished size (13). In addition, preoperative therapy makes response-evaluation of the primary tumor feasible prior to surgery (i.e., induction chemotherapy). It is also advantageous that the blood supply to the tumor remains, i.e., not altered by surgery. However, neoadjuvant therapy may change both tumor and recipient characteristics, leading to difficulties regarding surgical treatment (**Table 4**).

Postoperative adjuvant treatment has the potential to eradicate micro- or macroscopic tumor cells to improve survival, and to reduce the risk of both recurrence and metastases. In addition, features not available prior to surgery, such as complete histological evaluation, resection grade, and postoperative clinical status help further individualization of treatment, potentially increasing its efficacy and long-term survival for the patient (**Table 4**).

The Role of Adjuvant Therapies

Defining the role of adjuvant therapies for craniofacial malignancies is challenging. The rarity and varied pathology of

lesions in this anatomical region make it difficult to accrue large series of patients with uniform pathologies, and to date there are no randomized clinical trials to guide the treatment of patients with these malignancies. With only a few multi-institutional studies published, most reports in the literature are single-center series with limited numbers of patients and often short follow-up times, making results difficult to interpret and compare. In addition, treatment outcomes over long time-periods may be biased by medical and surgical developments. Selected publications providing relevant outcome measures are illustrated in **Table 5**.

PREOPERATIVE THERAPY

Paranasal Sinus Carcinoma

The role of preoperative radiotherapy is generally limited in patients with squamous cell carcinoma and adenocarcinoma of the paranasal sinuses as primary surgery provides a higher probability of radicality, lower complication rates, and also offers a precise histology with subsequent adjustment of postoperative radiation (14–17). Survival and local control in patients with advanced loco-regional tumors remain modest, with a meta-analysis showing an average 5-year survival of 51% (18). Radiation therapy alone or prior to salvage surgery should only be used when surgical resection is not feasible or is associated with unacceptable sequelae. Survival in such patients managed with primary radiation therapy with or without salvage surgery remains dismal (9–39%) (15, 17, 19, 20). If preoperative radiotherapy is used, a response-evaluation should be undertaken after 6–10 weeks to consider surgical resection of the tumor (14, 15, 17, 19–22).

The need to improve local control, increase survival and preserve organ function has prompted some centers to explore the addition of chemotherapy to standard treatment (23–26). Preoperative or induction chemotherapy can help to achieve operability in high-stage tumors, and can make radiation possible with less toxicity (23, 26, 27). The literature reports on a wide range of outcomes, and there are no definitive conclusions (28–30). Preoperative chemotherapy is usually not advised. There are concerns regarding possible disease progression during the treatment, and acquired cumulative toxicity leading patients being medically unfit for surgery (27). It can, however be considered in carefully selected cases where the tumor burden is so heavy that surgical resection or radiation is not possible without significant toxicity (27–29).

Sinonasal undifferentiated carcinoma and single-cell neuroendocrine carcinoma pose a unique therapeutic challenge to clinicians because of their aggressive biologic behavior, with a propensity (40–50%) for early invasion of vital structures such as the orbit, skull base, and brain, as well as a high risk of distant metastasis (20–30%) (31–35). In addition, these tumors are more chemo sensitive than other carcinomas in the same anatomical location (36, 37). Studies have documented the effect of platinum-based chemotherapy in these tumors, and intensive multimodal therapy is usually indicated, as oncological outcomes after open surgery remain poor (27, 36, 38, 39).

Patients with NUT-midline carcinoma—demonstrating loss of the ubiquitously expressed protein Integrase Interactor 1 (INI1; SMARCB1) —tend to present with large and locally advanced tumors; indeed, based on the previously reported series, most INI1-deficient sinonasal carcinomas are staged as T4 at the time of diagnosis. Experience suggests that these tumors respond well to neoadjuvant chemo-radiation (e.g., using a platinum based alkylating-like agent followed by radiation therapy) (40–45). Future treatments with agents that target the epigenetic machinery such as inhibitors against Enhancer of Zeste homolog 2 (EZH2) or histone deactylase may prove even more effective (46, 47).

Olfactory Neuroblastoma

The benefit of radical surgical resection in terms of survival is well–documented (27, 48–50), however, the role of preoperative radiotherapy is unclear. According to Yin et al. (51) preoperative radiation therapy can provide a valuable complement to surgery. Experience from University of Virginia shows that patients who responded to preoperative adjuvant therapy (radiotherapy for low-stage tumor and chemotherapy plus radiotherapy for high-stage tumors, respectively), had significantly lower rates of disease-related mortality (52, 53). Although there is no clear evidence supporting the administration of preoperative adjuvant therapy for all patients, preoperative platinum-based chemotherapy can be advocated for patients with locally advanced disease (e.g., with intracranial and/or orbital invasion) (54–65).

While radical surgery followed by postoperative radiation is considered the standard of care in adults, a similar approach in children can lead to significant long-term morbidity. Preoperative chemotherapy based multimodal approach should be considered in children with advanced stage disease, as pediatric olfactory neuroblastoma is considered a chemosensitive disease. Radiation therapy is effective for local control but lower doses should be considered in children (66).

Mucosal Melanoma

Preoperative radio-chemotherapy is generally not advocated for mucosal melanoma. However, radiotherapy may have a role when surgery is not appropriate or feasible (i.e., with palliative intent) (67–72).

Soft-Tissue Sarcoma

Preoperative radiotherapy may allow some patients with soft-tissue sarcoma to undergo potentially less mutilating surgery, and can also contribute to a higher rate of local control in groups of patients with a dismal prognosis. Preoperative treatment may also permit lower radiation doses and smaller target volumes than postoperative radiotherapy (73–76).

Preoperative chemotherapy is usually recommended for most patients with rhabdomyosarcoma, whereas its role in the management of other histological soft-tissue sarcoma subtypes is unclear at present (74–80).

TABLE 5 | Selected publications reporting outcome measures after multimodal treatment of craniofacial malignancies.

Publication	Histology	Treatment	5-year overall survival%	5-year progression free survival%
Waldron et al. (15)	SCC, AC, SNUC	XRT + S	39	41
Paulino et al. (17)	SCC, AdCC, AC, MEC	XRT only	0	18
		S + XRT	52	50
Le et al. (20)	SCC, AC, AdCC, SNUC	XRT only	19	20
		S + XRT	46	56
Jansen et al. (19)	SCC, AC, AdCC, SNUC	XRT + S	60	65
		XRT only	9	47
Tran et al. (21)	AC, AdCC, MEC	XRT + S	n/a	18
		S only	n/a	62
		S + XRT	n/a	9
Tiwari et al. (22)	SCC, AC, AdCC, MEC, SNUC	S + XRT	64	n/a
		XRT + ChT	37 (2-yrs)	n/a
Fernström et al. (26)	SCC, AC, AdCC, SNUC, NEC, MEC	ChT + XRT + S	54	32
Dulguerov et al. (18)	SCC, AC, AdCC, MEC, SNUC	S only	79	n/a
		S + XRT	66	n/a
		XRT only	57	n/a
Amit et al. (36)	SNUC	IC + ChT + XRT	66	74 (with response to IC)
		IC + S + XRT	43	55 (with response to IC)
Yin et al. (51)	ONB	XRT+ S	91	91
		S + XRT	79	82
		XRT only	50	63
Chao et al. (55)	ONB	S + XRT	67	87
		XRT only	n/a	51
		S only	n/a	0
Dulguerov et al. (61)	ONB	S + XRT	65	n/a
		XRT + ChT	51	n/a
		S only	48	n/a
		S + XRT + ChT	47	n/a
		XRT only	37	n/a
De Bonnecaze et al. (50)	ONB	S + XRT	73	n/a
		S + XRT + ChT	64	n/a
		S only	58	n/a
		ChT + XRT	32	n/a
		XRT only	29	n/a
		ChT only	53	n/a
Amit et al. (67)	MA	S + ChT + XRT	47	n/a
		S + XRT	42	n/a
		S only	39	n/a
		ChT + S + XRT	27	n/a
Samstein et al. (71)	MA	S + XRT	n/a	59
		S only	n/a	35
Benlyazid et al. (136)	MA	S + XRT	28	29
		S only	46	27
Kaur et al. (180)	M WHO II	S + XRT	68	54
	M WHO III	S + XRT	56	48
Aghi et al. (173)	M WHO II	S + XRT	n/a	100
		S only	n/a	44
Mair et al. (181)	M WHO II	S + XRT	n/a	60
		S only	n/a	50

(Continued)

TABLE 5 | Continued

Publication	Histology	Treatment	5-year overall survival%	5-year progression free survival%
Dziuk et al. (167)	M WHO III	S + XRT	n/a	80
		S only	n/a	15
Jasnau et al. (88)	OS	ChT + S	75	52
		Cht + S + XRT	80 (2-yrs)	n/a 60
		S only	67	
Mucke et al. (90)	OS	ChT + S	67	n/a
		S only	42	n/a
Kassir et al. (94)	OS	S only	46	n/a
		S + XRT	20	n/a
		S + ChT	50	n/a
		S + XRT + ChT	67 (2-yrs)	n/a

S, surgery; XRT, radiotherapy; ChT, chemotherapy; IC, induction chemotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; AdCC, adenoid cystic carcinoma; MED, mucoepidermoid carcinoma; SNUC, sinonasal undifferentiated carcinoma; NEC, neuroendocrine carcinoma; ONB, olfactory neuroblastoma; MA, melanoma; M, meningioma; OS, osteosarcoma; n/a, not available.

Atypical and Malignant Meningioma

The use of radiotherapy or chemotherapy as a primary therapy with or without surgery is generally limited to patients medically unsuited for surgery or to those who have unresectable disease (81).

Malignant Tumors of Bone and Cartilage

Although osteosarcoma is generally resistant to radiotherapy, proton-beam therapy may be useful in the treatment of chondrosarcomas and osteosarcomas that involve the skull base (82, 83). It can be particularly difficult to deliver sufficient radiation doses in cases of chondrosarcoma and chordoma due to nearby organs being at risk. Preoperative radiation therapy in these cases is generally not utilized (84–87).

Modern treatment regimens for classic osteosarcoma include preoperative chemotherapy to eradicate micrometastatic disease. Although its benefit in craniofacial osteosarcoma (CFOS) is controversial, preoperative chemotherapy has been associated with improved survival in patients with high-grade CFOS (88–97). Preoperative chemotherapy is not advocated in cases of chondrosarcoma and chordoma as these tumors are resistant (84, 86, 87).

POSTOPERATIVE THERAPY

Paranasal Sinus Carcinoma

Achieving radical resection in this anatomical location is challenging, and paranasal sinus carcinomas have a high tendency for local recurrence in the absence of postoperative radiotherapy (98). In general, adenocarcinoma (salivary gland type) is less sensitive to radiation therapy than squamous cell carcinoma. Salvage surgery may be warranted in recurrent cases, even when only close resection margins may be achieved. Postoperative radiotherapy is generally advised after non-radical surgery, or when radicality is questionable (14, 99–102). Adjuvant radiotherapy is widely used for stage T3 and T4 tumors, and has been effective in decreasing the incidence of local recurrence. However, there are no randomized trials or prospective comparisons, and the data in retrospective analyses are often based on older techniques (103–108). Commonly used conformal techniques include three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT). Charged particle therapy may offer additional advantages for delivering maximal tumor doses while minimizing radiation to the retina and brain (104–106).

The role of postoperative radiotherapy in cases of stage T2 tumors is unclear, while some studies show no benefit, others show higher recurrence rates in the absence of radiotherapy, especially in cases of high-risk tumors, such as adenoid cystic carcinoma and undifferentiated carcinoma (108–111). In cases of squamous cell carcinoma with macroscopic or microscopic tumors after surgical treatment, concomitant hypoxic modification with the radiosensitizer nimorazol should be used (112).

Postoperative chemotherapy has been incorporated as a component of the multimodal therapy of paranasal sinus carcinoma in a variety of ways. Concomitant platinum-based chemotherapy (cisplatin and 5-FU) seems to have a positive effect on local control and survival and may have an additional benefit in cases of non-radical surgery, advanced-stage disease, and extracapsular tumor extension (24, 27–29, 108, 113–118).

The prognosis of patients with recurrent or metastatic head and neck squamous cell cancer is generally poor. Carefully selected patients with a good performance status and locally recurrent disease may benefit from salvage surgery and/or re-irradiation (119, 120).

Systemic therapy is indicated for most patients with metastatic or advanced recurrent squamous cell carcinoma of the head and neck. The choice of systemic regimen—preferably administered as a part of a study protocol—is influenced by multiple clinical factors, including patient comorbidities, performance status, previous therapy, and pathologic features (i.e., programmed death-ligand 1 [PD-L1] expression status). Treatment options include immunotherapy with PD-L1 checkpoint inhibitors

(e.g., pembrolizumab and nivolumab), conventional cytotoxic chemotherapy (e.g., cisplatin and carboplatin) and molecularly targeted agents (e.g., epidermal growth factor receptor [EGFR] inhibitors cetuximab and panatimumab) (6–8, 121–130).

Olfactory Neuroblastoma

Surgical resection followed by radiation therapy is the most widely used approach in cases of olfactory neuroblastoma. The results with this approach are illustrated by Dulguerov et al. who conducted a literature review and meta-analysis that included 390 patients from 26 studies published between 1990 and 2000 (61). For the 169 patients treated with a combination of surgery and radiation therapy, the reported 5-year survival rate was 65%. The reported 5-year survival rates for the 87 patients treated with surgery alone and the 49 patients treated with radiation alone were 48 and 37%, respectively. A similar added benefit of radiotherapy over surgery alone was shown for high-grade tumors in a Surveillance, Epidemiology, and End Results (SEER) study of 281 patients treated from 1973 to 2010 (65).

Several studies have documented that even patients with locally invasive tumors can achieve favorable long-term survival when surgical resection is followed by radiation (48, 54, 58–64, 131). The use of a combined-modality approach is particularly important for patients in whom disease extends beyond the paranasal sinuses or in whom surgical resection margins are positive (54, 59, 62).

The role of postoperative chemotherapy for olfactory neuroblastoma is unclear. Although several studies have shown improved results, the reason for these results (i.e., whether it is surgery, radiation, or chemotherapy) is unclear (37, 50, 53, 132–135). In general, adjuvant chemotherapy with cisplatin and etoposid is advocated in all cases of sinonasal cancer with small cell histology (27, 50).

The rarity of olfactory neuroblastoma, combined with the favorable prognosis following aggressive local and regional therapy, has resulted in only very limited experience for patients with disseminated disease. Chemotherapy appears to have activity in some patients (particularly cisplatin and etoposide), and newer molecularly targeted approaches (e.g., using sunitinib or by activating the sonic hedgehog pathway), may become an option as the biology of these tumors is better understood (10, 11).

Mucosal Melanoma

Local recurrence occurs in 29–79% of cases with mucosal melanoma, despite aggressive surgery. Several series have reported an improvement in loco-regional control with postoperative radiotherapy; however, there is no verified impact on long-term survival and its role has not been established (68–72, 136–140).

There is only limited data available regarding the role and efficacy of postoperative chemotherapy in mucosal melanomas. A Phase II randomized trial of interferon vs. chemotherapy in Chinese patients with resected mucosal melanoma showed a superior effect of temozolamide and cisplatin, but these results require replication in a broader patient-population before postoperative chemotherapy can be considered a standard-of-care treatment for Western patients (141).

An understanding of the molecular pathogenesis of mucosal melanoma has provided important insights that are leading to the development of targeted therapies for specific subsets of patients with metastatic disease. Approximately 10% of mucosal melanomas harbor activating mutations in the BRAF gene and another 25% have somatic mutations or amplification of the tyrosine-protein kinase KIT (12, 142, 143). Several studies have reported durable tumor responses to KIT inhibition by imatinib, nilotimib, sorafenib, dasatinib, and sunitinib in patients with melanoma harboring KIT mutations (142, 144–148). In addition, checkpoint inhibitor immunotherapy (e.g., anti-CTLA4 and anti-PD-1 immunotherapy) has been shown to significantly prolong survival in some patients with cutaneous melanoma; however, additional investigation is necessary to clarify the role of these therapies in patients with mucosal melanoma (149, 150).

Soft-Tissue Sarcoma

The benefit of postoperative radiation therapy for most histologic subtypes of soft-tissue sarcoma of the craniofacial region is controversial. Experience from the literature argues in favor of radiotherapy in cases of large tumors, high-grade tumors, and low-grade tumors with positive or close (<1 mm) resection margins (78, 151–158). Although radiotherapy for adults is commonly delivered through external beam radiation, for children with small, critically located tumors in the head and neck, intracavitary or interstitial implants (brachytherapy) may be an option (154, 159).

The indication for postoperative chemotherapy in soft-tissue sarcoma has to be determined individually and is only established in certain histotypes and high-grade sarcomas (77–79).

Given the limited efficacy of conventional cytotoxic chemotherapy, soft-tissue sarcoma remains fertile ground for the field of drug development. Clinical trials in a number of areas have shown promise in metastatic soft-tissue sarcoma, either as single agents or in combination with chemotherapy (160, 161).

Atypical and Malignant Meningioma

Postoperative radiotherapy is advocated for all malignant meningiomas and subtotally resected atypical meningiomas of the craniofacial regions as complete surgical resection is generally difficult to achieve, and there is a high rate of both local recurrence and increased disease-specific mortality after non-radical surgery (81, 162–165). Data suggest that malignant meningiomas are associated with a recurrence rate 5 years after surgery of ∼60–90% and a 5-year overall survival of 20–50% (164–169). Adjuvant radiotherapy appears to decrease the recurrence rate by approximately half and may increase 5-year survival to >50%. For patients who undergo incomplete resection or biopsy of an atypical meningioma, the rate of recurrence or progression ranges from 60 to 100% (170, 171). Adjuvant radiotherapy improves local control, aims to prevent further neurologic morbidity related to growth of the residual tumor, and may improve survival (172).

The role of adjuvant radiotherapy is unclear in atypical meningiomas with an apparent gross total resection. The potential benefits of radiotherapy are more closely balanced with its risks and side effects, and it is particularly important to assess individual patient preferences and tolerance for risk (162, 170, 173–179). Based on contemporary series, the reported recurrence rate after imaging-confirmed gross total resection in patients not treated with adjuvant radiotherapy is ∼30–50% at a median of 5 years or less, with rates of failure trending higher with longer follow-up (173–175, 177). Most but not all observational studies suggest that adjuvant radiation therapy improves local control and progression-free survival after complete resection of an atypical meningioma (170–172, 177, 178, 180, 181). The impact of radiotherapy on overall survival is less clear, however, and most studies have included insufficient numbers of patients or length of follow-up to adequately assess this outcome. The potential benefits of radiation therapy should be weighed against the short- and long-term side effects and risks of this treatment method. Factors that increase the risk of side effects or delayed toxicities of radiation therapy include advanced age, low functional status, large treatment volume, and proximity of the radiation field to critical structures such as the optic pathways or pituitary gland.

The role of adjuvant postoperative chemotherapy for atypical and malignant meningiomas is unclear. Current guidelines of the National Comprehensive Cancer Network (NCCN) recommend three agents to treat patients with refractory and high-grade meningiomas: hydroxyurea, interferon-2B and sandostatin (long-acting release) (182, 183).

Malignant Tumors of Bone and Cartilage

Postoperative radiotherapy is generally not advocated after radical, *en bloc* excision of CFOS. After non-radical surgery, re-excision should be performed. Radiotherapy (together with chemotherapy) is normally used for patients who are not candidates for re-excision or where the surgical margins remain positive after this attempt (83, 89, 184–186). In contrast, postoperative radiotherapy is suggested for most patients with chondrosarcomas and chordomas as complete resection of the tumor is difficult and recurrent tumors are associated with poorer prognosis (84, 85). Proton-beam therapy may be particularly useful as photon therapy is associated with a high rate of local failure and carries a significant risk of brainstem and cranial nerve damage (187–189).

Modern treatment regimens for osteosarcomas at non-head and neck sites generally include systemic cisplatin-based chemotherapy to eradicate occult micrometastatic disease. While chemotherapy (given either postoperatively or preoperatively) improves the prognosis of extremity osteosarcoma dramatically, its benefit in osteosarcoma of the head and neck is controversial.

Postoperative combination chemotherapy has a clear role in the management of high-grade CFOS; however, prospective data to support a benefit from adjuvant chemotherapy in head and neck osteosarcomas are lacking. In uncontrolled case series, the use of adjuvant or neoadjuvant chemotherapy has been associated with improved survival in patients with head and neck osteosarcomas in some (88, 90–93) but not all series (89, 190). Two meta-analyses on this subject reported conflicting conclusions, possibly due to incomplete information on the influence of surgical margin status (94, 95).

Whether patients with low-grade osteosarcomas benefit from chemotherapy is unclear. Most low-grade jaw osteosarcomas may be adequately treated with surgery alone, as long as clear margins can be achieved (191). The decision whether to pursue chemotherapy for very small high-grade and very large low-grade tumors must be individualized and made on a case-by-case basis (88, 89, 91–93, 95).

Postoperative chemotherapy has no role in the treatment of chondrosarcomas and chordomas, and it is hoped that novel therapeutics like targeted therapy will benefit these patients (2, 86, 87, 192–195). The relative lack of efficacy of conventional chemotherapy and the discovery of novel signaling pathways in several histologic subtypes of chondrosarcoma have prompted interest in molecular-targeted therapies (e.g., imatinib, dasatinib, sirolimus), particularly for chemotherapy-refractory non-operable or metastatic tumors (196–198). A variety of molecular targets may be relevant therapeutically in chordoma, including platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), mammalian target of rapamycin (mTOR), and the *INI1* gene (2, 86, 87).

Management of the Neck in Sinonasal Cancer

Postoperative irradiation (or lymph node dissection) of the neck is advocated for all patients with cervical lymph node involvement, while elective prophylactic treatment (in node negative patients) is controversial, and the optimal management in these cases is uncertain (54, 61, 65, 103, 199, 200). Radiotherapy is usually not necessary if there is N1 disease without extranodal extension, and neck dissection has been completed (201–203).

DISCUSSION

Alongside developments in surgery, there have also been improvements in diagnostics, radiotherapy, and chemotherapy. Implementation of routine 3D treatment planning and IMRT allows delivery of higher radiation doses to the tumor while minimizing morbidity caused by irradiation of normal structures. At the same time, a better understanding of tumor biology allows the construction of more complex treatment strategies that incorporate adjuvant chemotherapy either pre or postoperatively. In the era of personalized targeted therapy, rapid strides are being made to identify specific tumor targets for the use of novel biologic agents, with the potential to change current management paradigms.

Management decisions are complicated by the rarity of these entities and the resulting lack of consensus regarding the optimal treatment regimen. Most studies suffer from a small number of patients and inconsistent treatment strategies. Although there is agreement that multimodal therapy is needed, the optimal sequence and combination of treatment modalities are not known. Inclusion bias is common upon assessment on treatment

outcomes, as patients with higher stage tumors are prone to be selected for combination therapy rather than surgery alone. In addition, reporting of survival function in the literature is not uniform, leading to difficulties with the comparison of results. In general, malignancies of the craniofacial region have a high tendency for local recurrence in the absence of adjuvant (postoperative) radiotherapy, even when the original resection was thought to be radical. Although there are no randomized trials, adjuvant radiotherapy is widely used and has been effective in decreasing the incidence of local recurrence (103). The effect of radiotherapy depends on tumor histology and is greatest in olfactory neuroblastoma, squamous cell carcinoma, and rhabdomyosarcoma, whereas the effect is less clear in adenocarcinoma and chondrosarcoma (204). Arguments for postoperative administration of radiotherapy (rather than preoperative) are as follows: a probably higher chance for local radicality; more precise evaluation of tumor volume and tumor margins; histology at primary surgery; and the possibility of more focused radiotherapy to reduce the danger of the dose affecting nearby organs at risk (205, 206). The use of radiotherapy alone or in combination with chemotherapy is generally limited to those who are medically unsuited for surgery or to patients with unresectable disease (207).

Advances in radiotherapy techniques have led to the development of highly conformal techniques that permit the delivery of therapeutic doses to the skull base while minimizing the dose to uninvolved vital structures (e.g., nerves, vessels, eyes). The most frequently used conformal techniques are 3D-CRT and IMRT (104, 208, 209). Charged particle irradiation (by proton beam or carbon ion) irradiation may offer additional advantages for delivering maximal tumor doses, while minimizing radiation to the retina and brain compared with photon-based therapy (105, 106, 210).

The role of chemotherapy in the treatment of craniofacial malignancies is unclear. Chemotherapy has been incorporated as a component of multimodality therapy with radiotherapy and/or surgery in a variety of ways; however, as there are no randomized trials, no definitive conclusions can be drawn about the impact of chemotherapy on outcomes.

A possible advantage of giving chemotherapy before loco-regional treatment (neoadjuvant) is more optimal drug delivery, permitting higher chemotherapy doses and dose intensities compared with chemotherapy given during or after local therapy. Possible disadvantages include a slow recovery from toxicity and, when the interplay between different modalities is less than optimal, delay of loco-regional treatment (still is the cornerstone of the intervention) may be fatally counterproductive (27).

Adjuvant chemoradiotherapy has been less studied. Craniofacial and sinonasal malignancies have generally not been included in trials evaluating the impact of chemotherapy as a radiosensitizer, and only limited experience has been gained from retrospective analyses (27).

This review shows that preoperative radiotherapy can have a documented role in the treatment of olfactory neuroblastoma and soft-tissue sarcoma, while preoperative chemotherapy can be advocated in the treatment of sinonasal undifferentiated carcinoma, neuroendocrine carcinoma, olfactory neuroblastoma, and craniofacial sarcoma (both soft-tissue and high-grade osteosarcoma). Postoperative radiotherapy has a well-established role in the treatment of most craniofacial malignancies, apart from mucosal melanoma. The role of postoperative chemotherapy is unclear in most histologies but is commonly used during the treatment of well-selected cases of paranasal sinus carcinoma, olfactory neuroblastoma, mucosal melanoma, soft-tissue sarcoma, and high-grade craniofacial osteosarcoma (**Figure 1**).

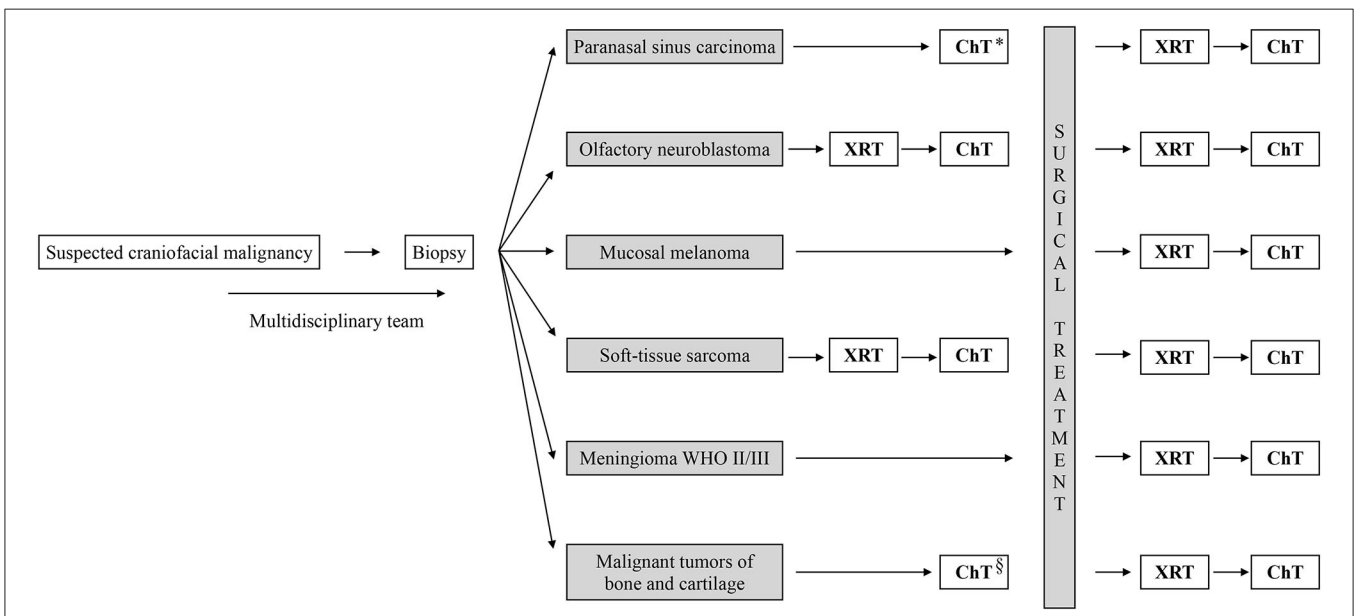

FIGURE 1 | Summary work flow diagram for adjuvant treatment of craniofacial malignancies. *Sinonasal undifferentiated carcinoma, neuroendocrine carcinoma and NUT-midline carcinoma. §High-grade osteosarcoma. XRT, radiotherpy; ChT, chemotherpy.

AUTHOR CONTRIBUTIONS

MK has conceived of the idea of the presented review, carried out a critical review of the literature, and wrote the manuscript. TM has supervised the review process. ØB, KS, ÅB, and TM have contributed to the final version of the manuscript with critical evaluation, suggestions, and expertise. All authors contributed to the article and approved the submitted version.

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Prognostic Impact of Tumor Extension in Patients With Advanced Temporal Bone Squamous Cell Carcinoma

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Objective: The extreme rarity of temporal bone squamous cell carcinoma (TB-SCC) has delayed the accumulation of high-quality clinical evidence. Our objective here was to explore anatomical factors associated with the prognosis of T4 TB-SCC cases.

Study Design: Case series with chart review.

Setting: Two academic tertiary care medical centers.

Subjects and Methods: The medical records of all TB-SCC cases were retrospectively reviewed in two institutions. The resulting data set contained 30 cases of primary T4 cancer eligible for initial definitive (curative) treatment. Disease-specific survival was calculated according to the Kaplan–Meier method. Cox proportional hazards model was used to identify anatomical prognosis factors.

Results: The disease-specific 5-years survival rate of 30 cases of T4 TB-SCC was 53.9%. The tumor invasion to the pterygoid muscle, posterior fossa dura, and sigmoid sinus and destruction of the ossicles were associated with poor prognosis in univariate analysis. The multivariate analysis reveals that the invasion of the ossicles, posterior fossa dura, and sigmoid sinus is an independent prognostic factor [hazard ratio (HR): 4.528 (95% CI: 1.161–17.658), $p = 0.030$; HR: 5.135 (95% CI: 1.616–16.315), $p = 0.006$; HR: 4.292 (95% CI: 1.385–13.303), $p = 0.012$]. The invasion of the carotid canal, petrous apex, middle fossa dura, otic capsule, pterygoid muscle, and middle ear had a high HR ($HR > 2$). The more invaded anatomical factors present in patients resulted in a poorer patient disease-specific prognosis, with a statistically significant difference.

Conclusions: Assessing which anatomical structures are susceptible to invasion by tumors may be important for predicting TB-SCC patient prognosis and selecting appropriate treatment planning, especially surgical intervention. In addition to previously reported factors, the destruction of the ossicles in the middle ear cavity can be an anatomical prognosis factor.

Keywords: squamous cell carcinoma, temporal bone, middle ear, external auditory canal, prognosis factor

INTRODUCTION

Malignant neoplasms of the temporal bone are extraordinarily rare and account for <0.2% of all head and neck malignancies (1). Squamous cell carcinoma (SCC) is the most common form of temporal bone malignant malignancies, followed by adenoid cystic, metastatic tumor, and mucoepidermoid carcinomas, among others. The low occurrence of temporal bone SCC (TB-SCC) has limited the amount of available data from both clinical and basic research. The Pittsburgh classification system is a globally popular staging system for TB-SCC, especially for the external auditory canal (EAC) carcinoma (1, 2). However, this scheme may not accurately reflect tumor extension and lumps resectable and unresectable tumors in the same category: T4. In the eight edition of the American Joint Committee on Cancer (AJCC) staging system, TB-SCC is not classified into a unique category and is considered a cutaneous SCC (3). Pensak et al. (4) reported clinical data from carcinomas with temporal origins using the University of Cincinnati Medical Center grading system for temporal bone tumors, which roughly considers anatomical tumor extension. In 1997, Kishimoto et al. (5) proposed a unique staging system that reflects the direction of tumor extension and invaded anatomical structures. However, the description is written in Japanese, and the system is thus not popular on a global scale. Kishimoto et al.'s (5) classification system, as shown in **Table 1**, does not reflect the impact of facial paralysis and the thickness of soft tissue invasion. Each classification system used previously has pros and cons (1–5). Until now, there has been no classification system that correlates invaded structures with the prognosis for patients with this malignancy. Therefore, based on these reports, the current global classifications, including the modified Pittsburgh classification, need reevaluating.

The complex, intricate structure of the temporal bone is due to its close associations with vital organs. Its anatomical structures, either in whole or in part, include the internal carotid artery (ICA), otic capsule, sigmoid sinus, jugular bulb, superior and inferior petrosal sinuses, internal auditory canal, the trigeminal and lower cranial nerves, and the eustachian tube. The temporal bone is surrounded by the dura of the middle and posterior cranial fossae, infratemporal fossa, temporomandibular

TABLE 1 | Previously reported classifications of temporal bone squamous cell carcinomas.

Clasification							
T		AJCC 8	(6)	(1)	(5)	T	(4)
I		Tumor smaller than 2 cm in greatest dimension	Tumor limited to site of origin, i.e. with no facial nerve paralysis and no bone destruction	Tumor limited to the external auditory canal without bony erosion or evidence of soft tissue extension	Tumor limited to the external auditory canal without bony erosion	I	Tumor in a single site, 1 cm or less in size
II		Tumor 2 cm or larger, but smaller than 4 cm in greatest dimension	Tumor extending beyond the site of origin indicated by facial paralysis or radiological evidence of bone destruction, but no extension beyond the organ of origin	Tumor with limited external auditory canal bony erosion (not full thickness) or limited (< 0.5 cm) soft tissue involvement	Tumor with limited external auditory canal bony erosion (not full thickness) or invasion of auricle	II	Tumor in a single site, >1 cm in size
III		Tumor 4 cm or larger in maximum dimension, minor bone erosion, perineural invasion or deep invasion	Clinical or radiological evidence of extension to surrounding structures (dura, base of the skull, parotid gland, temporomandibular joint, etc.)	Tumor eroding the osseous external auditory canal (full thickness) with limited (< 0.5 cm) soft tissue involvement, or tumor involving middle ear and/or mastoid	Tumor extends beyond the external auditory bony canal: mastoid cavity, tympanic cavity, fallopian canal, ossicles	III	Transannular tumor extension
IV	IVa	Tumor with gross cortical bone/marrow invasion	(Tx:) Patients with insufficient data for classification, including patients previously seen and treated elsewhee	Tumor eroding the cochlea, petrous apex, medical wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive soft tissue involvement (> 0.5 cm), such as involvement of temporomandibular joint or styloid process, or evidence of fasical paresis	Tumor involves the mandibular fossa, sigmoid sinus, jugular bulb, eustachian tube, petrous apex, inner ear, framen ovale. foramen lacerum, infratemporal fossa, carotid canal, parotid gland, temporal muscle, skin around auricle, etc.	IV	Mastoid or petrous air-cell invasion
	IVb	Tumor with skull base invasion and/or skull base foramen involvemen			Intracranial extension including dural invasion	V	Periauricular or contiguous extension (extratemporal)
						VI	Neck adenopathy, distant anatomic site, or infratemporal fossa extension

joint (TMJ), parotid gland, and parapharyngeal space. There are few studies examining the anatomical factors affecting the prognosis of advanced TB-SCC (1, 7). In this study, we examined the preoperative radiological findings of contrast computed tomography (CT) and magnetic resonance imaging (MRI) to reveal these factors in cases with T4 advanced TB-SCC.

MATERIALS AND METHODS

Ethics Statement

Our study was conducted with the approval of the ethics review committee of both Kyushu University Hospital (permit no. 29–43) and Fukuoka University Hospital (permit no. 2017M091).

Patients and Preoperative Staging

In this study, the tumor stages of cases were defined using the modified Pittsburgh classification. Clinical outcomes were analyzed for applicable patients treated at the Department of Otorhinolaryngology Head and Neck Surgery of two tertiary referral centers (Kyushu and Fukuoka University Hospitals) between April 2006 and December 2017. T4 cases that underwent definitive treatment and follow-up for at least 2 years after treatment were selected for this study. We used the Eastern Cooperative Oncology Group (ECOG) performance status scale to estimate the patients' physical functioning. All cases showed good performance status (PS), defined as PS 0–2 on the ECOG scale. Cases not undergoing treatment with sufficient intensity [either due to poor PS (with poor performance defined as PS 3–4) or patient refusal] were excluded. The final cases sampled for our retrospective cohort study consisted of 30 patients specifically diagnosed with T4 TB-SCC.

Prior to surgery, all cases underwent contrast-enhanced CT and MRI. Temporal bone CT images were obtained using a 64-detector-row CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan) or a 320-detector-row CT scanner (Aquilion One, Toshiba Medical Systems) with 0.5-mm collimation and a 512 × 512 matrix after an infusion of 2 ml/kg of a non-ionic iodinated contrast agent. Transverse scans were acquired in a plane parallel to the orbitomeatal plane in the helical mode with 120 kV, 250 mAs, 0.5-mm section thickness and overlap 0.3 mm with its adjacent slice, beam pitch 0.625, scan field of view (FOV) 240 mm, and display FOV 80 mm. MRI scans were performed on a 1.5-Tesla imaging unit (Achieva, Philips Medical Systems, Best, The Netherlands) or a 3-Tesla unit (Ingenia, Philips Medical Systems) with a 15-channel head array receiving coil for sensitivity encoding (SENSE) parallel imaging. Transverse T2-weighted images (TR/TE = 3,500/80 ms, FA = 90, 12 slices, slice thickness/gap = 2/1 mm, FOV = 170 mm, matrix = 304 × 238, NSA = 2), coronal T2-weighted images (30 slices, slice thickness/gap = 3/1 mm, FOV = 240 mm, matrix = 320 × 242, NSA = 2), and transverse T1-weighted images (TR/TE = 550/15 ms, FA = 90, 12 slices, slice thickness/gap = 2/1 mm, FOV = 170 mm, matrix = 224 × 181, NSA = 2) were acquired, followed by contrast-enhanced transverse T1-weighted images after intravenous injection of 0.1 mmol/kg of gadolinium-contrast agent. In addition, three-dimensional (3D) T1-weighted images (3D-FFE, TR/TE = 18/3.7 ms, FOV = 180 mm, matrix = 512 × 512, reconstruction thickness = 1 mm, NSA = 2) were acquired. 18-Fluorodeoxyglucose positron emission tomography (^{18}FDG PET)-CT with 4.0 MBq/kg of ^{18}FDG was performed to check for distant metastasis. At least two otorhinolaryngologists and two head and neck radiologists jointly assessed the extent of local progression and bone damage, confirming the T stage progression.

To examine anatomical prognosis factors, we examined 17 structures in the temporal bone among T4 TB-SCC patients, including the tympanic cavity, ossicles (the destruction of the ossicles in the middle ear), eustachian tube (the infiltration of the tympanic orifice in the eustachian tube), parotid gland, middle and posterior cranial fossae, petrous apex, carotid canal, jugular foramen (fossa), otic capsule, facial nerves (facial nerve paralysis), the TMJ, pterygoid muscle, parapharyngeal space, sigmoid sinus, endolymphatic sac, and styloid process (**Figure 1**).

Treatment Strategy

Our basic policy was to perform surgery for all resectable cases (T1–T4) that consented to treatment. Among the advanced T4 cases, induction chemotherapy or preoperative chemoradiation therapy (CRT) were selected to reduce tumor size if the tumor could not initially be treated with lateral temporal bone resection (LTBR). Radiotherapy was administered 5 days per week (1.6–2.0 Gy/fraction for a total dose of 30–40 Gy). Patients were scheduled for surgery if the tumor shrank to a resectable size as a result. If the tumor shrank sufficiently to be treated with LTBR, we performed LTBR rather than subtotal temporal bone resection (STBR). Inoperable cases were given curative CRT that targeted the primary tumor focus and lymph nodes. We selected a total dose of 60–70 Gy, including boost doses. Surgical intervention was considered if lesions shrank to a resectable size during CRT. Curative resections were followed by adjuvant CRT if a positive margin was confirmed.

For the first 4 weeks of radiation therapy (RT) (4 weeks, 1 week rest), patients were given intravenous 5-fluorouracil (5-FU; 250 mg/day) or oral S-1, a fluoropyrimidine anticancer drug (Taiho, Tokyo, Japan; tegafur equivalent = 65 mg/m^2) to potentiate the course's effects. Since 2015, instead of S-1, patients received triweekly cisplatin (CDDP: 100 mg/m^2, every 3 weeks, two to three cycles), a standard treatment for other head and neck SCCs (HNSCCs). We selected a docetaxel, cisplatin, and fluorouracil (TPF) regimen for patients as induction chemotherapy: 5-FU (600 mg/m^2; days 1–5) + CDDP (60 mg/m^2/day; day 1) + docetaxel (DOC: 60 mg/m^2; day 1) every 3 weeks for one to two cycles.

Statistical Analysis

The relationship between survival and the anatomical factors was examined using a univariate Cox proportional hazards model. We performed a multivariable analysis after adjusting for gender and age (≤65) as covariates. Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. All estimates below are the disease-specific 5-years survival (DSS) rate unless otherwise noted. The DSS rate was the same as the overall survival rate during our research period.

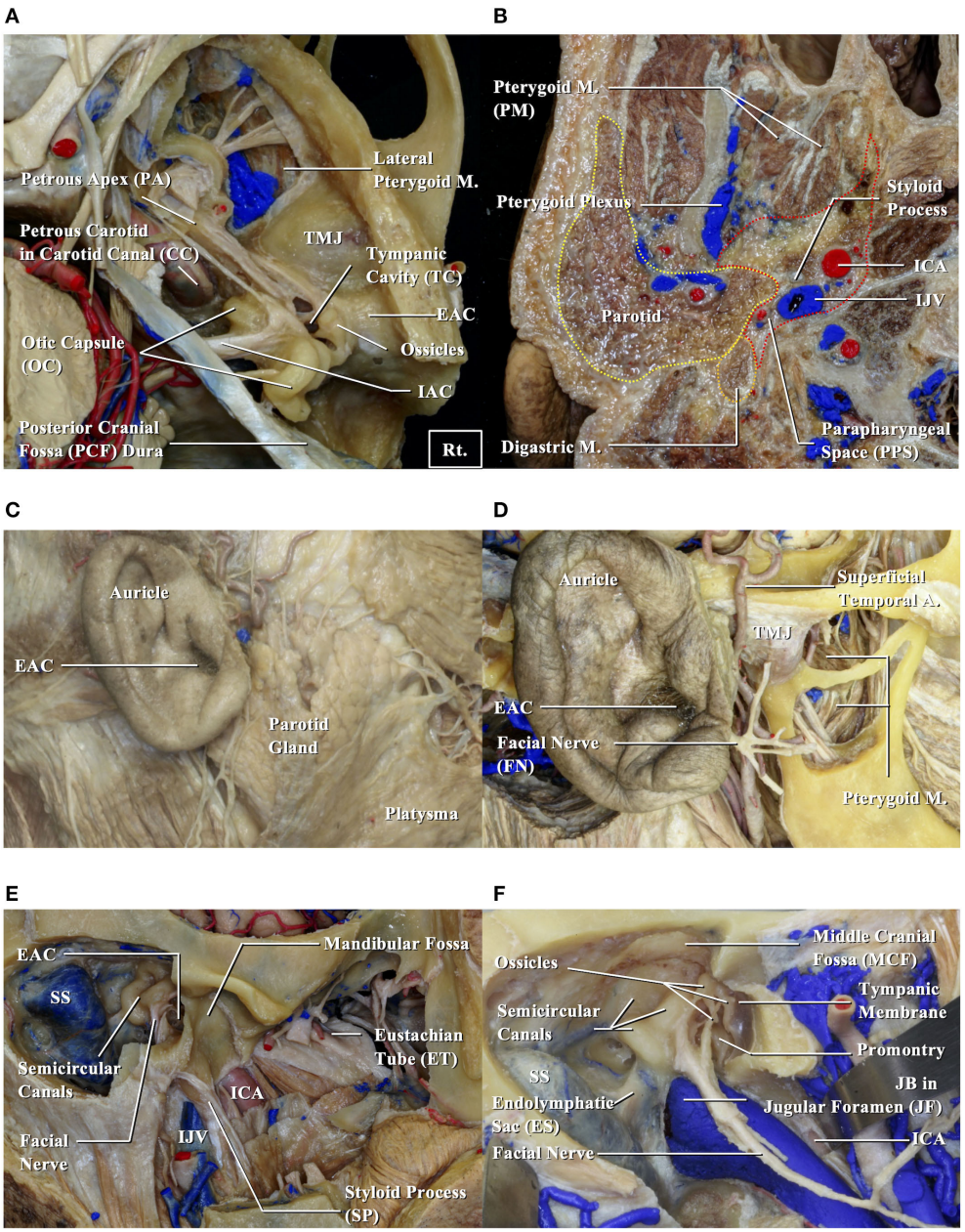

FIGURE 1 | Anatomical structures related to EAC squamous cell carcinomas. EAC, external auditory canal; ICA, internal carotid artery; IJV, internal jugular vein; JB, jugular bulb; M, muscle; SS, sigmoid sinus; TMJ, temporomandibular joint. **(A,B)** Cadavers are dissected from above **(A)** and below **(B)**. **(C)** Structures around the auricle are exposed. **(D)** Structures around the temporomandibular joint are exposed. **(E)** Structures related to the bony part of EAC are exposed. **(F)** Relationship between the middle ear and surrounding structures is shown.

JMP 6.1 was used for statistical analysis, and $p < 0.05$ indicated statistical significance.

RESULTS

Patient profiles are shown in **Table 2**. **Figure 2A** shows information on the invaded structures for all cases, and **Figure 2B** shows the DSS for all cases (53.94%). We then examined the relationship between invasion of the 17 anatomical landmarks and the prognosis of the patient. Univariate analysis for the anatomical prognosis factors identified invasion of the pterygoid muscle and posterior cranial dura and destruction of the ossicles and sigmoid sinus as significant predictors of poor prognosis (**Figure 3**). Extension into the otic capsule, petrous apex, middle cranial fossa dura, and carotid canal showed a high hazard ratio (HR > 2) but was not statistically significant ($p \geq 0.05$; **Figure 3**).

The Kaplan–Meier curves showed that cases with invaded ossicles, sigmoid sinus, pterygoid muscle, or posterior fossa

TABLE 2 | Patient profiles.

	N	%
AGE GROUPS		
<65	19	63
65≤	11	37
GENDER		
Male	10	67
Female	20	33
LYMPHNODE METASTASIS		
+	9	30
−	21	70
DISTANT METASTASIS		
+	0	0
−	30	100
PATHOLOGICAL FEATURE		
Poor. diff.	2	7
Mod. diff.	5	17
Well diff.	20	67
SCC with clear cell change or mucoepidermoid carcinoma	1	3
SCC with sarcomatoid change	1	3
Unknown	1	3
TREATMENT		
(C)RT+Surgery	14	47
Surgery	1	3
CRT only	10	33
iaChemo+CRT	3	10
Other	2	7
SURGICAL INTERVENTION		
LTBR	7	23
STBR	8	27
None	15	50

dura had a significantly worse prognosis than cases without the invasion of these structures ($p = 0.0055$, 0.0288, 0.0207, and 0.0202, respectively; **Figure 4**). The invasion of the tympanic cavity, middle fossa dura, petrous apex, carotid canal, and otic capsule was associated with decreased survival rates among the T4 cases, although this did not reach statistical significance (**Figure 4**). Results from the multivariate analysis for prognosis factors influencing the DSS rate among the T4 cases for TB-SCC are shown in **Table 3**. Invasion of the ossicles [HR: 4.528 (95% CI: 1.161–17.658), $p = 0.030$], posterior fossa dura [HR: 5.135 (95% CI: 1.616–16.315), $p = 0.006$], and sigmoid sinus [HR: 4.292 (95% CI: 1.385–13.303), $p = 0.012$] were independent prognostic factors. We divided cases into two groups: cases with invasion of at least one of these three structures and cases without invasion of any of these three structures. The Kaplan–Meier curves show that cases without invasion of any of the three structures had a significantly improved DSS rate compared to cases with invasion of any one of the three structures (90.91 vs. 29.41%, respectively, $p = 0.0022$; **Figure 5A**).

Finally, we examined the impact of the number of invaded structures. Univariate and multivariate analyses for prognostic factors influencing DSS rate showed that pterygoid muscle invasion could be regarded as an anterior/inferior invasion marker, ossicle invasion as a medial invasion marker, and posterior fossa dura or sigmoid sinus invasion as a posterior invasion marker. We found that the more factors present in patients resulted in a poorer patient disease-specific prognosis, with a statistically significant difference ($p = 0.008$). The DSS rates were as follows: 90.9% (no factor), 42.9% (one factor), 25% (two factors), and 0.0% (three factors) (**Figure 5B**).

DISCUSSION

The extreme rarity of TB-SCC causes a delay in building the high-quality evidence for its treatment. While no standard protocol has been established for its treatment, margin-negative resection is widely considered a viable treatment strategy for TB-SCC. Our treatment strategy for T4 cases included the induction chemotherapy or preoperative CRT to achieve *en bloc* and margin-negative resection. A few studies reported the effectiveness of preoperative CRT to achieve a high control rate after *en bloc* resection (8, 9). To control the residual lesions in cases with positive surgical margins, postoperative RT is reportedly an excellent strategy, (1, 4, 9, 10) as well as findings of the EORTC 22931 and RTOG 9501 trials in other HNSCCs (11, 12).

To examine the tumor extension accurately is necessary to achieve the margin-negative resection. A preoperative analysis of both contrast-enhanced MRI and CT is mandatory for determining the tumor extension of TB-SCC. High-resolution CT of the temporal bone is sensitive to bone erosion and can help define the extent of the mass using contrast enhancement (13). It is also essential to detect bone destruction (geographic, moth-eaten, or permeative pattern) in areas such as the jugular fossa, carotid canal, posterior and middle cranial bases, tegmen, TMJ, and petrous apex. Avascular labyrinthine bone is reported to be relatively unaffected in temporal bone malignancy (14). Bone resorption in certain areas should be suspected as signs of tumor invasion, which is often difficult to distinguish from inflammatory changes. Thus, once malignancy is suspected, a biopsy should be performed immediately. MRI is more effective for demonstrating associated soft tissue infiltration. TB-SCC often shows soft tissue invasion without any clear demarcation. Furthermore, on CT, it is difficult to distinguish between mucosal thickening and tumor in the middle ear without bone erosion. MRI before and after contrast enhancement provides excellent delineation of soft tissue tumor margins and infratemporal fossa and parapharyngeal space infiltration. Sagittal and coronal planes are helpful for demonstrating the contiguous involvement of the surrounding area. Most of the lesions appeared iso-intense on the T1-weighted image and heterogeneously hyper-intense on the T2-weighted image (15). Heterogeneous enhancement can be found due to necrosis. Contrast-enhanced MRI is the best sequence for identifying dural invasion, which shows thickening of the dura and nodular contrast enhancement (15).

The relationship between tumor extension and patient prognosis is important to consider with surgical intervention

A

Case	Age	Gender	TC	Ossicles	ET	Parotid	MCF	PCF	PA	CC	JF	OC	FN	TMJ	PM	PPS	SS	ES	SP	DSS (Months)	Follow-up
1	55	M	+	+	+	+	-	+	-	-	-	+	+	+	-	+	+	+	+	66	NED
2	65	M	+	+	+	+	-	-	-	-	-	+	-	-	-	-	-	-	-	14	DOD
3	72	M	+	+	+	+	+	-	+	+	+	-	+	+	+	+	-	-	-	18	DOD
4	51	F	+	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	66	NED
5	66	F	+	-	+	-	-	-	-	-	-	+	-	+	-	-	-	-	-	66	NED
6	57	M	+	+	+	+	-	-	-	-	-	+	-	+	-	+	-	-	-	11	DOD
7	40	F	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	-	-	22	DOD
8	75	M	+	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	-	4	DOD
9	62	M	+	+	-	+	-	-	-	-	-	+	-	+	-	+	-	+	+	66	NED
10	73	F	+	+	+	+	+	-	+	+	+	+	-	-	-	+	-	-	+	66	DOC
11	58	M	+	+	-	-	+	+	-	-	-	+	-	-	-	-	+	-	-	5	DOD
12	86	F	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	+	10	DOD
13	38	M	+	-	+	+	+	-	-	-	-	-	-	+	-	-	-	-	-	66	NED
14	62	F	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	66	NED
15	48	F	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	9	AWD
16	65	F	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	45	NED
17	56	F	+	-	+	+	-	-	-	-	-	-	-	+	-	-	-	-	-	45	NED
18	53	F	+	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	129	NED
19	78	F	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	91	NED
20	64	F	+	-	-	-	+	+	-	-	+	-	-	-	-	-	+	-	-	111	AWD
21	57	F	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	66	NED
22	67	F	+	-	+	+	-	-	-	-	+	-	-	-	-	-	-	-	-	106	NED
23	60	F	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	+	13	DOD
24	49	F	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	97	NED
25	38	F	+	-	+	+	-	+	-	+	+	-	-	-	+	+	+	-	+	15	DOD
26	55	F	+	+	+	+	+	+	+	+	+	-	-	-	+	+	+	+	+	19	DOD
27	59	M	+	+	-	+	+	+	+	+	+	+	+	-	-	-	+	+	-	7	DOD
28	74	M	+	-	+	-	+	+	+	+	+	-	+	-	-	-	+	+	-	20	DOD
29	65	F	+	+	-	+	+	+	-	-	-	+	-	-	-	-	+	-	-	5	DOD
30	48	F	-	-	-	+	-	-	-	-	-	-	-	-	-	+	-	-	-	13	NED

B

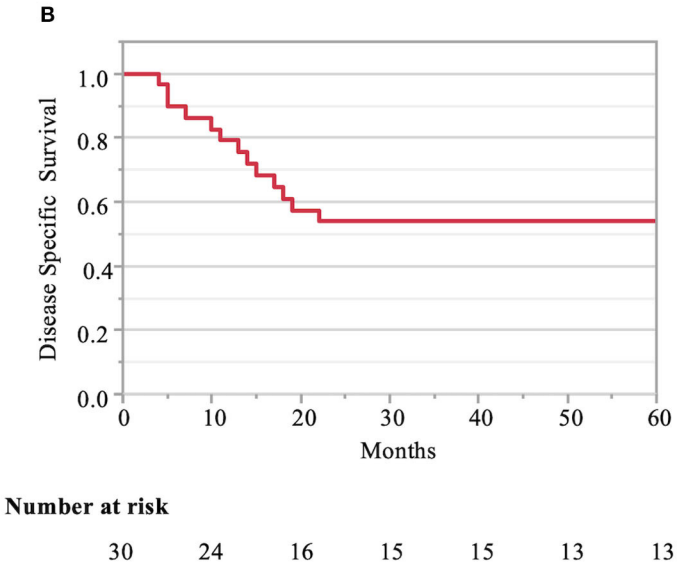

FIGURE 2 | Detailed information on the invaded structures (17 landmarks) **(A)** and disease-specific 5-years survival curve in all T4 cases **(B)**. Anatomical factors examined include the tympanic cavity (TC), ossicles (the destruction of the ossicles in the middle ear), eustachian tube (ET; the infiltration of the tympanic orifice of the eustachian tube), parotid gland, middle and posterior cranial fossae (MCF and PCF), petrous apex (PA), carotid canal (CC), jugular foramen (fossa) (JF), otic capsule (OC), facial nerve (FN; facial nerve paralysis), temporomandibular joint (TMJ), pterygoid muscle (PM), parapharyngeal space (PPS), sigmoid sinus (SS), endolymphatic sac (ES), and styloid process (SP).

	Invasion site	Number	%	HR (95% CI)	p value
1	Tympanic Cavity	24	80.0	2.519 (0.327 - 19.389)	0.375
2	**Ossicles**	14	46.7	5.165 (1.415 - 18.849)	**0.013**
3	Eustachian Tube	17	56.7	1.414 (0.434 - 4.604)	0.566
4	Parotid Gland	21	70.0	1.409 (0.388 - 5.125)	0.602
5	Middle Fossa Dura	15	50.0	2.846 (0.873 - 9.271)	0.083
6	**Posterior Fossa Dura**	11	36.7	3.469 (1.131 - 10.638)	**0.030**
7	Petrous Apex	8	26.7	2.412 (0.808 - 7.201)	0.115
8	Carotid Canal	8	26.7	2.122 (0.709 - 6.350)	0.179
9	Jugular Foramen	10	33.3	1.392 (0.466 - 4.155)	0.554
10	Otic Capsule	12	40.0	2.180 (0.731 - 6.504)	0.162
11	Facial Nerve	6	20.0	1.333 (0.365 - 4.872)	0.663
12	TMJ	10	33.3	0.722 (0.221 - 2.352)	0.589
13	**Pterygoid Muscle**	4	13.3	3.759 (1.123 - 12.577)	**0.032**
14	Parapharyngeal	13	43.3	1.561 (0.524 - 4.655)	0.424
15	**Sigmoid Sinus**	10	33.3	3.175 (1.061 - 9.504)	**0.039**
16	Endolympatic Sac	7	23.3	1.521 (0.468 - 4.945)	0.486
17	Styloid Process	8	26.7	1.087 (0.334 - 3.536)	0.889

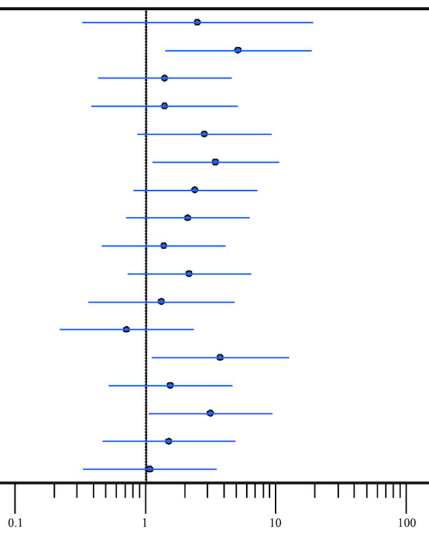

FIGURE 3 | Anatomical factors predicting survival (univariate analysis) using a forest plot.

for advanced TB-SCC. Several classification systems for TB-SCC have been designed (**Table 1**), each with their own pros and cons. The field would benefit from a modified Pittsburgh staging system that aligns with surgical procedures by more explicitly considering extension range. Other HNSCC, laryngeal, or pharyngeal carcinoma use a staging system that reflects the

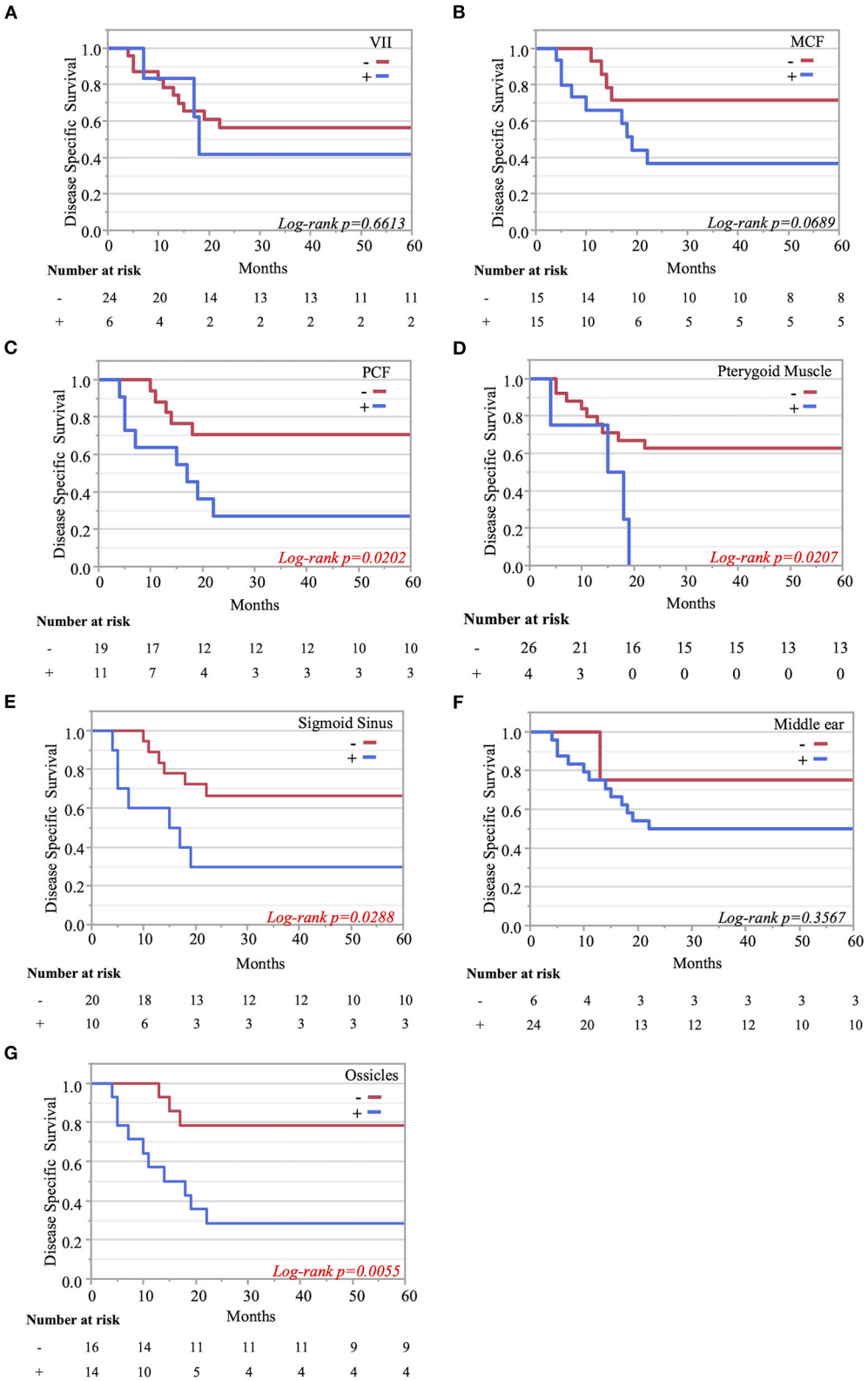

FIGURE 4 | Kaplan–Meier curves. Disease-specific 5-years survival curves according to tumor invasion of the facial nerve **(A)**, middle cranial fossa **(B)**, posterior cranial fossa **(C)**, pterygoid muscle **(D)**, sigmoid sinus **(E)**, middle ear **(F)**, and ossicle destruction **(G)**.

tumor extension. For TB-SCC, establishing such a staging system would help to standardize the treatment strategies. The rarity of this tumor type makes it difficult to examine anatomical prognosis factors, so we can only discuss these factors using a few cases and limited clinical experience. Furthermore, many investigators have grouped tumors with different histologies in the same analysis and used origin sites other than the temporal bone, such as secondary temporal bone invasion from the parotid cancer and auricle (16, 17), which make the results from these studies difficult to interpret. In this study, we focused on the analysis of advanced TB-SCC.

In the modified Pittsburgh classification system, extensive soft tissue involvement (>0.5 cm) was considered T4 (1). However, the two types of cases that can be treated with either LTBR or STBR for curative resection are placed into the same category: T4. Therefore, it is difficult to accurately predict prognosis (8). Ito et al. (18). pointed out that soft tissue involvement does not correlate with prognosis. We hypothesized that the invaded anatomical structures are more important in predicting prognosis than the thickness of the soft tissue. Identifying anatomical prognostic markers is necessary to establish an appropriate staging system. Many surgeons consider the extent of tumor invasion to be associated with prognosis. However, it is difficult to collect enough advanced T4 cases in a single center for sufficient statistical analysis. Therefore, in this study, we analyzed the relationship between tumor extent and patient DSS rate with 30 T4 TB-SCC cases from two tertiary referral centers.

The most common site of TB-SCC is the external auditory meatus. The bone and cartilage of the EAC and tympanic membrane can be a barrier to tumor diffusion. However, tumors easily cross this barrier and extend inferiorly and anteriorly through the bone–cartilage junction, the fissures of Santorini, and the foramen of Huschke (dehiscence) located anteroinferior to the osseous EAC and posteromedial to the TMJ (19). However, it is well-known that TB-SCC, representing EAC SCCs, arises from various sites and demonstrates a multidirectional pattern of growth with and without bony invasion.

If the tumor extends medially, the otic capsule, petrous apex, carotid canal, and jugular bulb may be invaded. The bone plates over many structures, such as the jugular bulb, carotid tegmen, fallopian canal, and labyrinth, are thin and hence vulnerable to tumor erosion (20). Inferior extension of the tumor results in invasion of the parapharyngeal space, including the carotid sheath, which surrounds the ICA, internal jugular vein, and lower cranial nerves. The invasion of the ICA makes curative resection impossible. Posterior extension of the tumor reaches the posterior cranial fossa dura following mastoid air cell destruction. Superior extension easily invades the middle cranial fossa dura through the middle ear due to the thin roof of the middle ear. If the origin of the SCC is the middle ear or if the

TABLE 3 | Anatomical factors predicting survival (multivariate analysis).

Invasion site	Multivariate analysis				
	HR	p-value	95% CI		
Ossicles	4.528	**0.030**	1.161	-	17.658
Posterior fossa dura	5.135	**0.006**	1.616	-	16.315
Pterygoid muscle	2.902	0.099	0.819	-	10.284
Sigmoid sinus	4.292	**0.012**	1.385	-	13.303

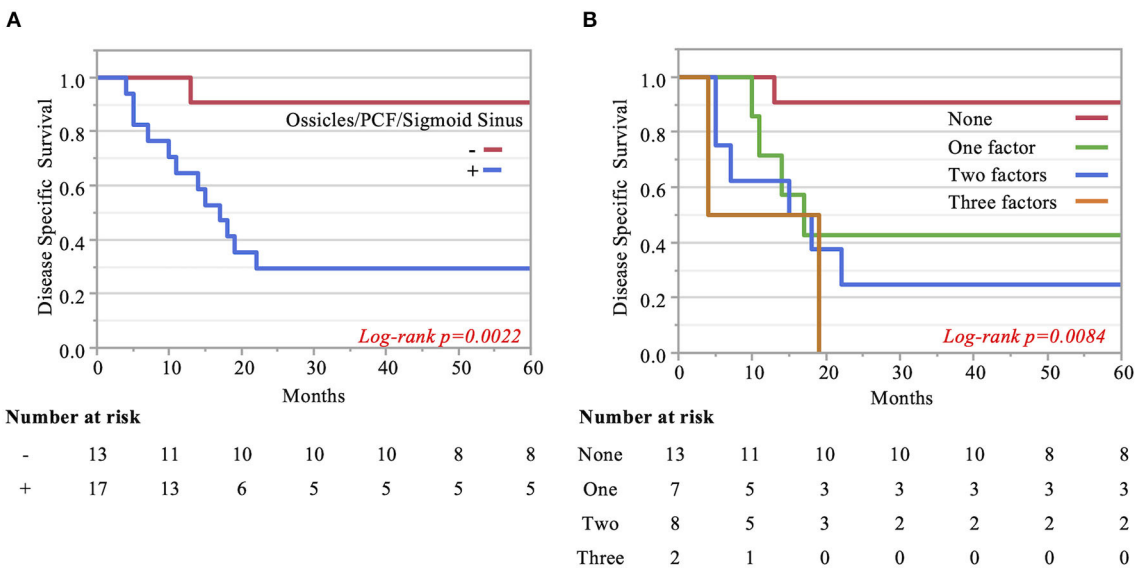

FIGURE 5 | Kaplan–Meier curves. **(A)** Two groups are compared: cases with invasion of at least one of the three significant structures and cases without invasion of any of these three factors. **(B)** Pterygoid muscle invasion, ossicle destruction, and invasion of the posterior fossa dura/sigmoid sinus are regarded as an anterior/inferior invasion marker, medial invasion marker, and posterior invasion markers, respectively. The impact of the number of invasion markers was analyzed among all three categories. The more markers, the poorer the patient disease-specific prognosis, which was statistically significant.

EAC SCC extends into the middle ear, the tumor easily invades the middle cranial fossa dura. Previous studies show that bony invasion (18, 21, 22); facial paralysis (6, 18, 23); and invasion of the middle ear (21), dura (20, 21, 24), petrous apex (25), jugular foramen (25, 26), ICA (22), and TMJ (24) are associated with a poor outcome.

In this study, our univariate analysis showed that the invasion of the pterygoid muscle, posterior cranial fossa, and sigmoid sinus worsens prognosis. The invasion of the otic capsule, petrous apex, middle cranial fossa dura, and carotid canal tends to decrease the DSS rate. Specific anatomical invasions, which make margin-negative resection difficult, tend to be an anatomical marker for clinical deterioration.

The superior head of the pterygoid muscle is attached to the anterior disk of the TMJ, and the inferior head of the pterygoid muscle inserts on the mandibular condyle. Our univariate results show that the pterygoid muscle is associated with prognostic factors. Omura et al. (24) reported that TMJ invasion was a prognostic marker because it makes achieving local control difficult. Our study showed that pterygoid muscle invasion, rather than TMJ invasion, was associated with prognosis. In our series, TMJ involvement without pterygoid muscle invasion can be resected with a negative free margin, but more medial tumor invasion can lead to a greater possibility of positive margin resection. Furthermore, if the tumor extends anteriorly to reach the TMJ, this results in invasion of the abundant venous network around the TMJ and pterygoid muscle (pterygoid venous plexus). The invasion of the venous plexus could serve as a route for metastasis spread.

The middle ear invasion upgrades the T stage to T3 according to the modified Pittsburgh classification (1). Middle ear invasion is considered a marker for poor patient prognosis (21). However, some authors have reported that middle ear invasion does not worsen prognosis, and there is a relatively good survival rate for T1–T3 TB-SCC (8, 9). Therefore, it is still uncertain whether middle ear invasion is a prognostic factor. Stell and McCormick (6) suggested it is surprising there was no difference in survival between external and middle ear tumors when considering the tumor origins; prognoses for cases with tumors in the external auditory meatus and middle ear are similar when comparing similar stages of tumors. Manolidis et al. (23) reported the clinical results of 81 cases with temporal bone malignancies. In their study, patients with epithelial malignancies and moderate or total facial paralysis showed a significant survival disadvantage, and anterior tumor spread carried a worse prognosis than middle ear spread, although the numbers were too low to show statistical significance. Tumors involving the middle ear are not necessarily equivalent to a poor outcome (23). Our results support these findings. Interestingly, destruction of the ossicles in the middle ear significantly worsened prognosis, in contrast to middle ear invasion. Therefore, the destruction of the ossicles could be an anatomical prognostic factor that may reflect the molecular and biological characteristics of the tumor responsible for accelerating bone destruction. This finding is new, and further work is needed to conclude whether it is a true anatomical prognostic factor.

Many authors continue to discuss the impact of dural invasion on prognosis (7, 16, 25, 27–29). In 1994, Parasad et al. reported that in cases where dural invasion was present, surgical resection did not improve overall survival after comparing 11 dural invasion cases with resection and nine dural invasion cases without resection. However, they did not adequately study the margins of resection (16). Furthermore, Leonetti et al. (7) mentioned that dura mater and brain invasion represent aggressive biological behavior. Further, some authors reported that dural involvement and intracranial disease did not affect disease-free survival (16, 27, 28). Kawahara et al. (25) reported that of eight cases that had dural invasion suspected preoperatively and who underwent complete resection with a wide safety margin, only one of the eight cases had apparent brain invasion. Dural involvement from preoperative imaging studies did not affect long-term tumor control and survival (25). Seligman et al. (29) argued that dural invasion need not automatically be considered a surgical contraindication in all cases, noting that three of their four cases of TB-SCC survived for over 5 years following STBR. In our study, the invasion of the posterior cranial fossa dura significantly worsened the DSS rate (27.27%), and invasion of the middle cranial fossa dura showed a high HR (HR = 2.846). These results suggest that dural invasion is a prognostic factor. However, if dural invasion can be accurately assessed and *en bloc* negative margin resection achieved, this does not deny the potential for improving the prognosis. However, the number of such cases is considered a limiting factor.

For vascular invasion, invasion of the sigmoid sinus significantly worsened the DSS rate (30.0%), and invasion of the carotid canal showed a high HR in our study (HR = 2.122). Michaels and Wells (30) found tumors penetrating through the bony wall of the middle ear and infiltrating the carotid canal. For extensive infiltration, radical surgical procedures are contraindicated. Parasad et al. (20) reported that two out of four cases showing invasion of the carotid artery died within 2 years, with several authors supporting these findings of poor DSS rates in cases with vascular invasion (20, 31, 32). Based on our findings, we consider that main vessel invasion could be a prognosis factor.

Facial nerve paralysis has been associated with a poor clinical outcome (6, 18, 23), confirming why cases with facial paresis or paralysis are categorized into T4 in the modified Pittsburg classification (1). However, in an analysis of 147 T4 cases from 21 studies comparing cases with and without facial nerve paralysis, Higgins and Antonio (33) concluded there was no significant impact to overall survival and DSS. In our study, facial nerve paralysis was not associated with prognosis. We surmise that our department's policy of aggressive surgical intervention greatly contributed to improved prognoses among facial paralysis cases. Sacrificing the facial nerve leads to a poorer quality of patient life, but aggressive resection of the facial nerve for cases with facial paralysis is worth considering for local control (18).

We found that the prognosis of cases without any invasion of the ossicles, posterior fossa dura, or sigmoid sinus, which

were identified as independent markers, was dramatically better. In addition, a greater number of anatomical prognosis factors resulted in poorer patient DSS rates, a difference that was statistically significant. Therefore, both the anatomical site and number of structures affected are thought to be closely related to prognosis. Recently, multidisciplinary collaboration among clinicians in neurosurgery, otorhinolaryngology, and plastic surgery departments within surgical teams, as well as technological advances in surgical equipment and more precise diagnostic imaging, has removed some of the barriers to the challenging negative surgical margin procedure and improved the prognosis of TB-SCC patients. Therefore, classification measures for invasion of anatomical structures will be important in the future.

A staging system reflecting tumor extension that correlates with clinical prognosis is important for understanding prognosis and selecting an appropriate treatment strategy. Establishing the staging system requires accumulating and analyzing large data sets on anatomical tumor extension and prognoses. Applying the new staging system in our study was not possible due to the low sample size. Furthermore, we cannot completely exclude the influence of the treatment modality on our results. Therefore, detailed data sets published from a number of institutions will be necessary to build a large database for this rare cancer.

CONCLUSIONS

Assessing which anatomical structures are susceptible to invasion by tumors may be important for predicting TB-SCC patient prognosis and selecting appropriate treatment planning, especially surgical intervention. In addition to previously reported factors, the destruction of the ossicles in the middle ear cavity can be an anatomical prognosis factor. A large data set with detailed information regarding the extent of the tumor from various institutions will help facilitate future retrospective meta-analyses.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics review committee of Kyushu University Hospital (#29–43) and the ethics review committee of Fukuoka University Hospital (#2017M091). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NK and TNa contributed to the study design (patient selection, statistical analyses). NK contributed to writing of the drafts of the manuscript. MM, TNo, NA, and RU contributed to patient inclusion and follow-up. MM, KSat, TH, KK, and RK contributed to collecting the clinical data of patients. NK, TNo, KSag, and AH contributed to data analysis. All authors contributed to critical reading, revision of the manuscript, and approval of the submitted version.

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REVIEW
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Methods of Skull Base Repair Following Endoscopic Endonasal Tumor Resection: A Review

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Following the introduction of fully endoscopic techniques for the resection of pituitary tumors, there was a rapid expansion of the indications for endonasal endoscopic surgery to include extrasellar tumors of the skull base. These techniques offer significant advantages over traditional open surgical approaches to the skull base, including improved tumor resection, and better post-operative neurological outcomes. Following their introduction, however, the initial rate of post-operative CSF leak was unacceptably high. Post-operative CSF leak following skull base surgery is a major source of morbidity, and can lead to the development of life-threatening intracranial infection. The use of vascularized naso-septal flaps transformed the management of these patients, significantly reducing the rate of post-operative CSF leak and increasing the number of patients that could benefit from this less invasive treatment modality. Adequate repair of iatrogenic defects in the skull base is of crucial importance for patients with skull base tumors, as the development of a post-operative CSF leak, and the associated complications can significantly delay the administration of the adjunctive oncological therapies these patients require. In this review, we provide an overview of the latest evidence regarding skull base reconstruction following endoscopic skull base surgery, and describe the skull base repair technique in use at our institution.

Keywords: skull base, endoscopic, CSF leak, nasoseptal flap, lumbar drain, pituitary, meningioma, chordoma

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INTRODUCTION

The endoscopic endonasal approach to the skull base was initially introduced as an adjunct to the microscope in the resection of pituitary tumors in 1979, with fully endoscopic approaches described in the early 1990s (1–3). The endoscope has since come to supersede the operative microscope in pituitary surgery, due to the improved visualization offered as a result of a wider field of vision, better illumination of the operative field and the ability to inspect anatomical areas using angled endoscopes that are impossible to see using the microscope (4, 5). Following the adoption of this technique for the resection of pituitary tumors, it was adapted for resection of extrasellar skull base lesions (6–9). Fully endoscopic approaches are now in widespread use in the management of malignancies of the ventral skull base, including esthesioneuroblastoma, chordoma, and chondrosarcoma, as well as aggressive, locally invasive pathologies such as meningiomas, and craniopharyngiomas (10–14).

The advantages of these extended endonasal approaches (EEA) to skull base tumors are that they provide a direct trajectory to lesions of the ventral skull base, avoiding the parenchymal retraction and the traversal of cranial nerves inherent to transcranial approaches for these tumors. This less invasive approach is associated with better neurological outcomes and a shorter length of stay than more traditional open approaches (15, 16). When used in the management of chordomas and esthesioneuroblastomas, the endoscopic approaches offer higher rates of gross total resection than their transcranial alternatives (14, 17). However, early series utilizing these approaches were complicated by post-operative CSF leak rates as high as 40%, and this shortcoming was regarded as a major obstacle in their widespread adoption (18). Post-operative CSF leak is the major source of morbidity following endoscopic skull base surgery, and can lead to the development of meningitis and/or hydrocephalus (19, 20). Moreover, CSF leak leads to longer length of stay and increases the chances of unplanned readmission to hospital following surgery, both of which have the potential to delay, or interrupt adjunctive therapy in patients with skull base malignancies (21, 22).

The resection of pituitary adenomas is often an extra-arachnoidal procedure, with a small dural defect created to access the pathology and is therefore associated with a low rate of CSF leak that was not observed to increase following the introduction of the endoscopic technique (23). EEA to skull base malignancies, however, necessitate larger bony and dural defects, causing high flow intra-operative CSF leaks which are demonstrably associated with higher rates of post-operative CSF leak (24). Therefore, the reconstruction of the skull base following extended EEA to the skull base is of paramount importance in avoiding post-operative CSF leak. Advances in skull base reconstruction, particularly the use of vascularized local flaps, have greatly reduced the incidence of this complication and have been instrumental in the expansion of these approaches for the management of skull base malignancy (25). The importance of using vascularized flaps as part of a multi-layer, rather than a monolayer closure of skull base defects to prevent post-operative CSF leak has also been highlighted in a recent study by Simal-Julián et al. (26). In this review, we will provide an overview of the latest methods used to reconstruct large skull base defects leading to high flow CSF leaks following tumor resection, as well as describing our preferred method for the repair of these defects.

DISCUSSION

Skull Base Reconstruction Methods

Pedicled Nasoseptal Flap

The development of the naso-septal flap (NSF) in by Hadad et al. in 2006 revolutionized the field of endoscopic endonasal skull base surgery and has facilitated the expansion of this treatment modality (27). Prior to its development, skull base repair was undertaken using multilayered techniques employing autologous fat grafts and synthetic dural substitutes as inlay and onlay grafts secured with fibrin glue, which could be supported by the intranasal placement of Foley catheters (28). As mentioned above, this repair technique was associated with an unacceptably high rate of post-operative CSF leak and the requirement for an alternative technique was clear. The NSF consists of a vascularized mucoperichondrial/periosteal flap harvested from the midline nasal septum and pedicled on the posterior septal branch of the sphenopalatine artery. This allows for the creation of a large flap, capable of covering skull base defects extending from the frontal sinus to the sella antero-posteriorly, and spanning the width of the distance between both orbits. This vascularized flap was used in combination with an inlay synthetic collagen graft and an autologous fat graft, secured using fibrin glue. In a series of 44 patients undergoing endoscopic skull base surgery involving large dural defects and high flow intra-operative CSF leaks, the authors reported a post-operative CSF leak rate of 4.5% (27). In the setting of very large skull base defects, involving the anterior and posterior cranial fossa, bilateral NSF have been harvested to effectively prevent CSF leak (29).

This technique was widely adopted soon after its introduction, and Kassam et al. published their experience of NSF utilization in 75 patients following EEA to a variety of skull base tumors. A large dural defect with high flow intra-operative CSF leak was noted in 55 patients. In similar fashion to that reported by Hadad et al. the authors combined the nasoseptal flap with the use of an inlay synthetic dural graft, secured using a biological glue or Foley catheter. In the first 1/3 of the series, the authors noted a post-operative CSF leak rate of 33% in cases with a high-flow intra-operative CSF leak rate, which dropped to 5.4% in the latter 2/3 of the series (30). With craniopharyngiomas in particular, the authors noted in a separate publication that the use of a NSF dramatically decreased the rate of post-operative CSF leak from 58 to 5% (31). As a testament to the versatility of this technique, it has also been successfully utilized following EEA to skull base lesions in pediatric cohorts, in spite of initial concerns regarding the small size of the nasal septum in children (32, 33). Certain skull base tumors, such as craniopharyngiomas, chordomas and chondrosarcomas have a propensity for local recurrence, necessitating revisional surgery for further tumor resection. NSF can be successfully re-used in this setting, by dissecting it from the initial defect site and re-applying it in the standard fashion, with no increase in the rate of post-operative CSF leak (34). Traditional open approaches to skull base tumors are often closed with local vascularized pericranial flaps, and the options for skull base defect repair in the setting of a post-operative CSF leak can be limited. The use of an endoscopically harvested NSF to successfully control CSF leak following open skull base surgery has been reported, expanding the repertoire of this technique even further (35).

Although the development of the NSF was a significant advance in skull base surgery, the technique itself is subject to some limitations. Although it is a rare occurrence, the flaps are subject to necrosis due to compromise of the vascularized pedicle: this is reported to occur in <1% of cases, but these patients will often require revisional surgery for alternative skull base reconstruction (36, 37). The removal of the mucosa from the nasal septum leaves a large defect, that heals by secondary intention over an extended period. This process

TABLE 1 | Table summarizing the results of studies using a vascularized nasoseptal flap following EEA and intra-operative CSF leak.

Author, Year	Technique	Number of Cases	Post-operative leaks (%)
Hadad et al., 2006 (27)	Collagen inlay graft ± fat graft + NSF + fibrin glue + nasal packing/Foley catheter	44	2 (4.5)
Kassam et al., 2008 (30)	Collagen inlay graft ± fat graft + NSF + dural sealant + nasal packing/Foley catheter	55	8 (14.5)
Zanation et al., 2009 (71)	Collagen inlay graft + NSF ± fat graft + DuraSeal® + Gelfoam® nasal packing/Foley catheter	70	4 (5.7)
Luginbuhl et al., 2010 (43)	Dual layer "button" fascia lata graft + NSF + dural sealant + Nasopore®	16	1 (6.3)
Liu et al., 2012 (61)	Fascia lata graft inlay/overlay graft ± fat graft + Surgicel® ± fascia lata + NSF + Merocel® tampon	93	3 (3.2)
Garcia-Navarro et al., 2013 (42)	Fat graft + onlay fascia lata + MEDPOR/Bone + NSF + DuraSeal® ± Lumbar Drain	21	1 (4.7)
Thorp et al., 2014 (37)	NSF ± middle turbinate graft (no further details provided)	144	3 (2.1)
Cavallo et al., 2019 (44)	Fat graft + NSF + Merocel® tampon	25	1 (4)
Conger et al., 2019 (67)	Fat graft + collagen sponge + MEDPOR/Bone + NSF + Fat graft + collagen sponge + dural sealant + Merocel® tampon	83	4 (4.3)

can lead to significant nasal crusting and a perception of nasal obstruction in the ipsilateral nostril (38). More significant structural abnormalities of the nose can also occur, such as septal perforations and collapse of the nasal dorsum, with the rates of these complications varying from 1 to 14% in the published literature (37, 39, 40). Overall, the use of a NSF for skull base reconstruction can lead to additional morbidity due to the sinonasal complications associated with this technique. A recent review of over 700 patients who underwent endoscopic skull base surgery found that the use of a NSF conferred additional sino-nasal morbidity post-operatively, and had a negative impact on the sino-nasal quality of life outcomes of patients (41).

The NSF is an effective, versatile technique that has gone on to form the basis of skull base reconstruction protocols in a number of high-volume skull base centers the world over, with some modifications which will be explored in the sections that follow. **Table 1** summarizes the results of the use of the NSF within skull base reconstruction protocols following EEA and resection of skull base tumors.

Gasket Seal Technique

Long-term outcomes from a series of 46 patients who underwent EEA and skull base reconstruction using the gasket seal technique were published by Garcia-Navarro et al. in 2013 (42). This technique involves the placement of an autologous fat graft to eliminate intracranial dead space, covered by an autologous fascia lata graft over the bony skull base defect, with the fascial graft sized such that it extends 1 cm beyond the defect circumferentially. Following the placement of this graft, an autologous bone graft, or synthetic polyethylene implant is laid over the fascial graft, sized to fit snugly inside the bony defect. In the latter stages of their series, the authors then placed a NSF over this solid buttress, secured with DuraSeal (Confluent Surgical, United States). In 67% of cases, this repair technique was combined with a 24–48 h period of prophylactic lumbar drainage. In the cases where the gasket seal technique was combined with a NSF, the authors reported a post-operative CSF leak rate of 4.7%. The authors commented that as the solid buttress they use is not curved, this technique is suboptimal for the closure of large skull base defects that cross two geometric planes (e.g., anterior skull base and clivus).

Bilayer Button Technique

This technique, originally described by Luginbuhl et al. in 2010 utilizes a bilayer fascia lata graft, in conjunction with a NSF. In this method, the authors suture an onlay fascia lata graft slightly larger than the bony defect onto a much larger piece of fascia lata that goes on to act as an inlay graft. The inlay graft is directly opposed to the dura, with the appropriately sized onlay graft acting to prevent graft migration from the dural defect. This fascial construct was then covered in 16/20 cases by a NSF, secured with a fibrin glue. Using this technique, the authors noted a decrease in the rate of post-operative CSF leak in patients with large dural defects from 45 to 10% (43). Although the authors introduced the sutured fascia lata construct at the same time as the NSF, given the results from other series, it is highly likely the greatest contributor to the decreased rate of post-operative CSF leak was the NSF.

The 3F Technique

Cavallo et al. recently published a modification to their skull base reconstruction technique following EEA, having previously employed a modification of the gasket seal technique combined with a NSF (10). In this modification, which the authors call the 3F technique, the first F (fat) is the placement of an autologous fat graft into the dead space created by tumor resection, which acts to span the entirety of the osteodural defect, secured with fibrin glue. The second F (flap) is the placement of the NSF, bolstered with cellulose sponges, and secured with nasal tamponades for 72 h. The authors mobilize the patient to a sitting position as soon as possible after surgery and they are encouraged to walk and stand as much as possible, the third F (flash). Using this skull base reconstruction protocol, the authors reported a post-operative CSF leak rate of 4% in 25 patients who had large osteodural defects following EEA (44). Post-operative lumbar drainage was not used.

Alternative Options

In situations where the pedicled NSF is not available, for example when sinonasal malignancies invade the nasal septum or pterygopalatine fossa, or when the patient has undergone previous reconstruction with a NSF, alternative vascularized regional flaps are available. The lateral nasal wall flap is harvested

from the opposite side of the nasal cavity to the NSF, and is based on the lateral nasal wall artery, a branch of the sphenopalatine artery. In a series of 24 patients with high flow intra-operative CSF leaks, Lavigne et al. reported a post-operative CSF leak rate of 25% (45). Although at first glance this figure appears to be high, it should be borne in mind that this reconstructive method was used as a salvage method, after necrosis of an existing NSF or when the a NSF was not available, having been used in previous surgery. The authors comment that the lateral nasal wall flap cannot cover as great a surface area as the NSF, and due to the fact it is harvested from the conchal surfaces of the lateral nose, it has a greater "memory" and may migrate from its intended position more often. When local vascularized reconstruction options are not available, due to extensive tumor invasion/previous radiotherapy, or where the expertise in vascularized flap reconstruction does not exist, avascular free grafts are an option. In this technique, layered reconstruction of the skull base defect created following EEA is undertaken using a variety of autologous and non-autologous dural substitutes. In a large series of EEA to skull base tumors, Roxbury et al. reported a post-operative CSF leak rate of 6.85%, using a multi-layer closure consisting of an underlay layer of synthetic dural substitute or fat graft, an overlay layer of dural substitute and a further overlay layer of Alloderm® (Lifecell, United States) acellular matrix in combination with a free mucosal flap (46). However, the authors noted that on multi-variate analysis that a high-flow CSF leak, as is often generated in EEA to skull base tumors, was associated with a higher rate of post-operative CSF leak and the majority of the cases in their series were pituitary adenomas, which are known to be associated with a lower rate of post-operative CSF leak (31). More convincing evidence of the potential efficacy of free graft reconstruction techniques is provided by a recent study published by Matavelli et al., wherein the authors describe the results following the resection of 186 sinonasal malignancies, resulting in large anterior cranial fossa defects. Using autologous iliotibial tract and fat tissue in a three-layer reconstruction protocol, the authors reported a post-operative CSF leak rate of 5.8% (47). Although these studies do suggest that acceptable results can be obtained with the use of free graft techniques, in the absence of a trial comparing both techniques, the weight of the evidence suggests that lower rates of CSF leak are obtained with the use of local vascularized flaps, and this view is supported by the results of a systematic review comparing the efficacy of skull base reconstruction methods following EEA (48). A further reconstruction option in the context of unavailability or unsuitability of the NSF is the endoscopic pericranial flap. This technique, originally described by Zanation et al., involves the minimally invasive, endoscopic harvesting of a pericranial flap through a small scalp incison. This flap is then brought through into the nasal cavity via a bony defect drilled in the nasion (49). Following this, it can be used to cover osteodural defects in an identical manner to the NSF and it has been successfully utilized in the reconstruction of anterior and posterior fossa skull base defects (50, 51).

In the setting of previous radiotherapy to the skull base, resulting in delayed CSF leak, transposition of a temporo-parietal fascial flap pedicled on the superficial temporal artery has been utilized (52, 53). This involves harvesting of the flap through an external skin incision overlying the temporal fossa, which is then transposed through the infratemporal fossa into the nasal cavity via an endoscopic *trans*-maxillary sinus or *trans*-pterygoid approach. Although there are reports of its success, the requirement for an external skin incision, as well as the risk of injury to the frontal branch of the facial nerve mean this approach is uncommonly used, and reserved for when local flap options are unsuitable.

In the setting of locoregional flap failure, the use of free myo-cutaneous flaps, facilitated by microvessel anastomosis to reconstruct skull base defects following EEA has been described. Kang et al. have described the successful use of a vastus lateralis flap, pedicled on the descending branch of the lateral femoral circumflex artery in four patients with anterior skull base defects following EEA. In all four cases, initial locoregional flap methods failed to adequately reconstruct the skull base and the vastus lateralis flap was employed as a salvage procedure, whereby the facial artery was used as a recipient vessel and the flap was tunneled through a maxillotomy to cover the skull base defect (54). These techniques have also been utilized in the repair of posterior fossa defects following EEA; the radial forearm free flap has been employed effectively to reconstruct a cranio-cervical junction defect following EEA for a clival chordoma. Similar to the four cases above, the patient had undergone previous attempts to reconstruct the skull base using a NSF (55). The use of free flaps for the reconstruction of the skull base following EEA is a significant undertaking, requiring complex mutli-discplinary input and in our view should only be considered when loco-regional reconstruction methods have failed.

Adjuncts to Skull Base Repair

Lumbar Drainage

The value of post-operative lumbar drainage of CSF following EEA to the skull base has been the source of debate since the introduction and widespread adoption of these approaches. The initial high rate of post-operative CSF leak with EEA prompted some centers to adopt lumbar drainage as a matter of course following EEA, providing observational evidence for their efficacy (56). Others called into question the necessity of lumbar drainage when a NSF is used, and suggested they may in fact be harmful, citing the risk of meningitis, CSF over-drainage and spinal headache and longer hospital stay with their use (57–59). In reality, the heterogeneity of the skull base repair methods in these studies, as well as their observational nature leaving them highly susceptible to selection bias, limited the conclusions that could be drawn from them.

The requirement for a randomized controlled trial, with clearly defined inclusion criteria and controls in place for selection bias was clear, and the results from such a trial were published in 2018. In this trial, published by Zwagerman et al. all patients undergoing EEA resulting in a dural defect >1 cm^2 along with extensive arachnoid dissection and/or entry into a ventricle were eligible for recruitment (60). Patients were randomized to drain or no drain after the completion of skull base

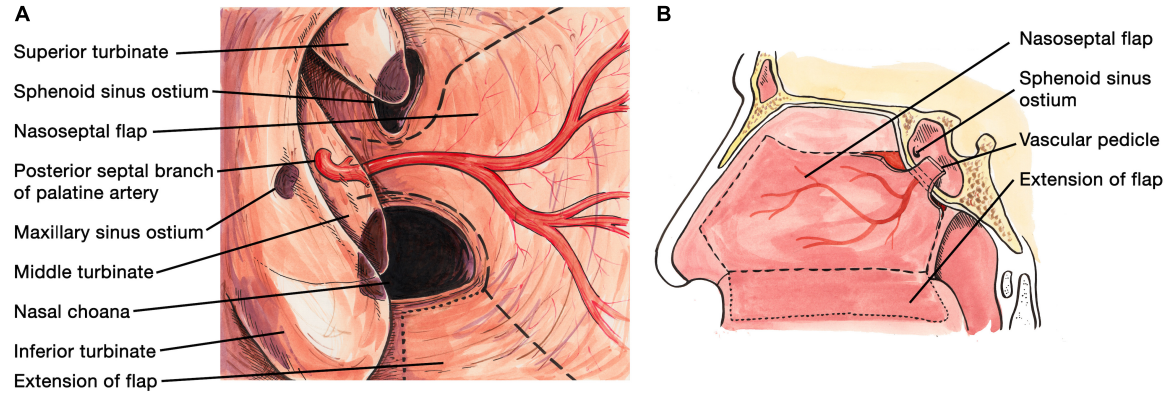

FIGURE 1 | (A) Diagrammatic representation of the endoscopic view during harvesting of the naso-septal flap via the right nostril. An incision is made 1–2 cm below the cribriform plate along the mucosa of the nasal septum. A further incision is made along the medial aspect of the floor of the nasal cavity, which can be extended further medially (dotted line) if a large naso-septal flap is required. Both incisions are then connected by an anterior vertical incision. The flap is then dissected from the nasal septum in retrograde fashion and stored in the nasopharynx or maxillary sinus, to be used for skull base reconstruction at the end of the case. **(B)** Sagittal view of the boundaries of the nasoseptal flap, with the dotted line indicating an optional extension of the incision if a large flap is required.

reconstruction, with the lumbar drain placed in the operating room and left in place for 72 h, draining 10 ml/h. All patients had skull base reconstruction with a local vascularized flap. The trial was terminated early having recruited 170 patients, due to evidence of benefit in the lumbar drain arm of the trial. 18/85 (21.2%) of patients with no drain suffered a post-operative CSF leak compared with 7/85 (8%) of patients who had a lumbar drain placed. There were no instances of meningitis associated with lumbar drain use, and only two patients developed spinal headache requiring a blood patch. There was also no significant increase in the risk of venous thromboembolism in the patients who had a lumbar drain placed. In a subgroup analysis based on lesion location, the authors concluded that there was a significant decrease in the incidence of post-operative CSF leak with use of a lumbar drain in patients with pathology located in the anterior and posterior cranial fossa, but that patients with tumors in the suprasellar area did not benefit from lumbar drain insertion. The authors suggested this may have been because the vascularized local flaps used are most effective in the suprasellar region, but they may not provide enough coverage to cover larger defects anteriorly and posteriorly. The results from this trial are striking, but should be interpreted with caution given that this a single center study where one skull base reconstruction protocol is used; the applicability of these results to centers utilizing different methods of skull base repair are uncertain. Moreover, the rates of post-operative CSF leak in both groups were higher than those previously reported in defects closed with vascularized local flaps, and the authors did not provide any data on length of stay in the two cohorts (27, 30, 42). Despite the shortcomings of this trial, it is likely that there are a subset of patients at particularly high risk of CSF leak that stand to benefit from "prophylactic" lumbar drain insertion.

Direct Support of Repair

Following the positioning of the materials used in the skull base reconstruction, the majority of authors would advocate some form of physical support for the reconstruction, to allow time for epithelisation of the defect and for the mucosa of the NSF to integrate with the mucosa adjacent to the operative site. A number of series have utilized the placement of a Foley catheter with the balloon inflated to provide an upward pressure on the skull base repair, whereas others use nasal tampons or inflatable Merocel® (Medtronic, United States) sponges (30, 61, 62). Prior to the insertion of any buttressing material, the use of tissue sealants to secure the NSF to the skull base is commonplace, although Liu et al. argue that this is not required and merely contributes to unnecessary surgical costs (30, 42, 62, 63).

A further technique to provide support for skull base reconstructions following EEA that has been suggested is the suturing of an onlay fascia lata graft to the edges of the dural defect, following the placement of an inlay synthetic dural substitute in the subdural space and combined with a NSF. Xue et al. found that the rates of post-operative CSF leak decreased following their implementation of this practice, although this was confounded by the fact that there was a significantly higher rate of intra-operative lumbar drain insertion in the group with dural suturing (64). The requirement for dural suturing has also been reported in endoscopic re-intervention for post-operative CSF leak, but at present there is no evidence to support its routine use in all EEA for skull base tumors or for its superiority over non-suture techniques (42, 65).

Skull Base Repair: The Dublin Technique

In our center, we employ a standardized method of skull base reconstruction for all EEA as well as endoscopic *trans*-sphenoidal approaches to pituitary tumors, even in the absence of an intra-operative CSF leak. Following the establishment of this protocol, we have reported a post-operative CSF leak rate of 1%, although this was higher in the early part of the senior author's experience prior to the introduction of this standardized technique, in keeping with the experience of other surgeons (30).

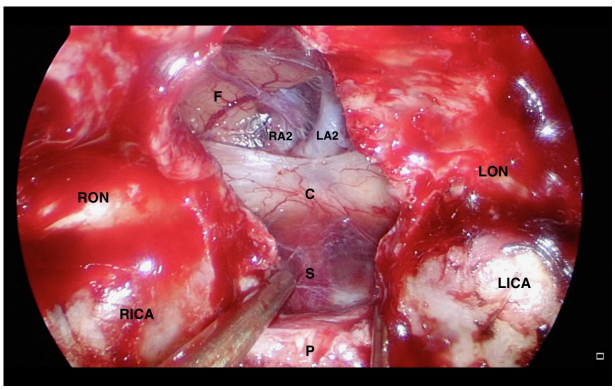

FIGURE 2 | Intra-operative endoscopic view of the skull base defect following a *trans*-tubercular approach to a planum sphenoidale meningioma. C: Optic Chiasm, F: Frontal Lobe, LA2: A2 segment of left anterior cerebral artery, LICA: Left Internal Carotid Artery, LON: Left Optic Nerve, P: Pituitary Gland, RA2: A2 segment of right anterior cerebral artery, RICA: Right Internal Carotid Artery, and RON: Right Optic Nerve.

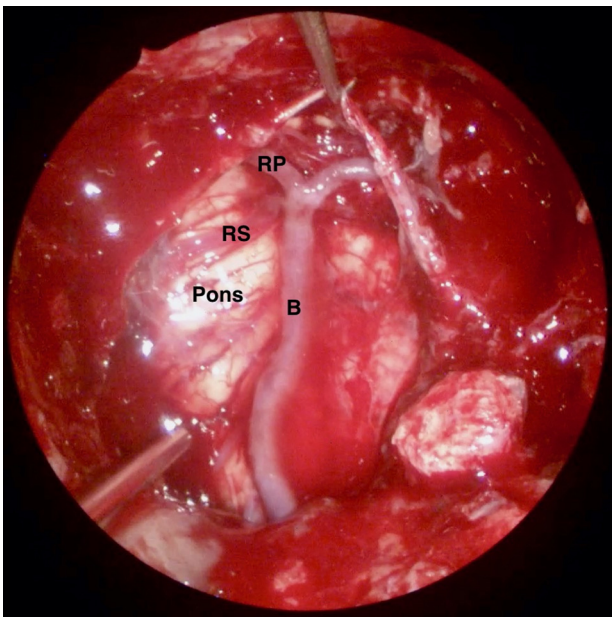

FIGURE 3 | Intra-operative endoscopic view of the skull base defect following the resection of a clival chordoma. B: Basilar Artery, RP: P1 segment of right posterior cerebral artery, and RS: Right superior cerebellar artery.

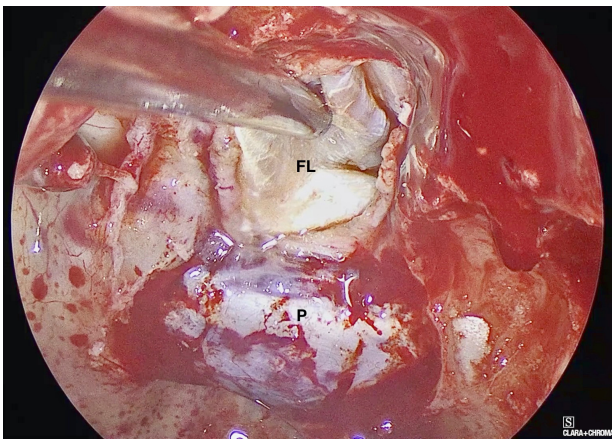

FIGURE 4 | Intra-operative endoscopic view demonstrating the placement of the inlay fascia lata graft. FL: Fascia Lata, P: Pituitary Fossa Dura.

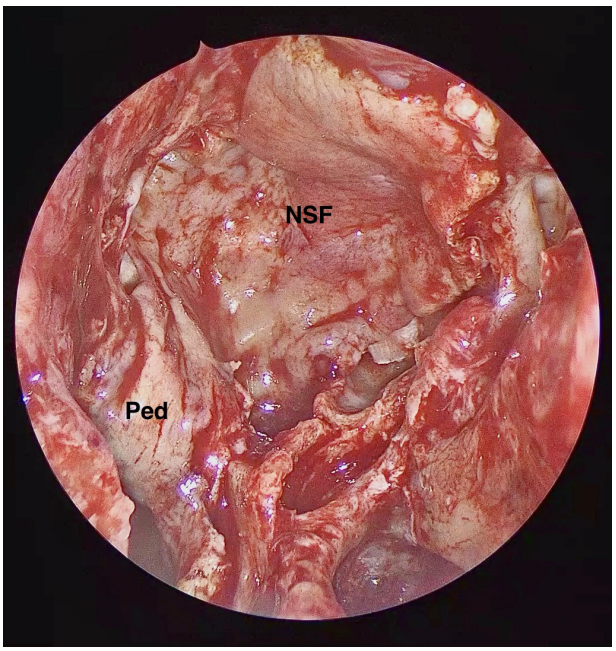

FIGURE 5 | Intra-operative endoscopic view demonstrating the naso-septal flap placed to cover the osteo-dural defect in its entirety. NSF: Nasoseptal flap, Ped: Vascular Pedicle.

In the latter third of a series of 270 patients (operated between July 2006 and June 2016) undergoing endoscopic surgery for resection of pituitary and skull base tumors, 1/90 (1%) patients experienced a post-operative CSF leak. When only EEA with high flow intra-operative CSF leaks were repaired using the following technique, 1/28 (4%) of patients experienced a post-operative CSF leak (66).

A NSF flap is harvested at the beginning of the procedure, and stored in the posterior nasopharynx/maxillary sinus until completion of the tumor resection. **Figure 1** is a diagrammatic representation of the harvesting of a NSF at the beginning of the procedure. Following tumor removal, an inlay graft of autologous fascia lata is inserted in the subdural space, and is sized to be larger than the osteodural defect in all dimensions. The only fascia lata donor site complication in our series was one case of wound hematoma requiring evacuation in a patient with Cushings disease (1/28, 4%). **Figures 2**, **3** are intra-operative photographs demonstrating the variety of skull base defects that can be closed using this technique. Placement of the fasica lata as an inlay larger than the dural opening ensures that the

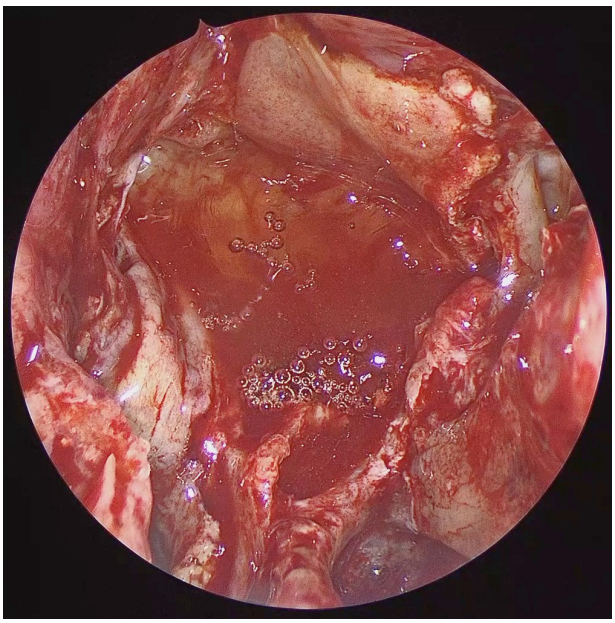

FIGURE 6 | Intra-operative endoscopic view of the naso-septal flap secured with dural sealant.

graft does not migrate out of the defect, and that it is opposed to the dura mater with each CSF pulsation. This intradural fascial layer is not secured using sutures/clips and contrary to concerns raised by some authors, we have not noted any issues regarding migration of the graft material (43). We then place the vascularized NSF directly over the dural and bony defects, with no intervening exogenous material. We avoid placing any intervening material between the dura and the NSF because in our view, natural tissues with good blood supply are more likely to adhere to each other and any intervening material may hinder this. The NSF is then covered with a further layer of fascia lata, and the entire construct is secured with dural sealant. Our preferred dural sealant is Bioglue® (CryoLife, Inc., United States). **Figures 4–6** demonstrate the major components of our skull base repair technique. We do not insert further bolstering materials (Foley catheters, nasal tampons) and we do not use any prophylactic lumbar drains. Prior to the adoption of this technique in 2013, we utilized a fat graft, covered with an onlay graft of dural substitute/fascia lata secured with dural sealant. In the setting of a high flow intra-operative CSF leak, a post-operative CSF leak was noted in 7 of 20 cases (35%) (66).

Our technique is different from the Gasket-seal technique, insofar as an inlay rather than an onlay fascia lata graft is used, and is more similar to the bilayer button technique and indeed that originally described by Hadad et al. in that respect (27, 42, 43). **Figure 7** allows for a comparison of the two major alternatives to our technique. We also diverge from the protocol of Conger et al. who argue that a solid buttress is required for the closure of high flow intra-operative CSF leaks (67). The other published series that most closely resembles our method is that of Eloy et al., describe the use of a NSF to cover an initial layer of autologous fat, fascia lata or dural substitute, secured with dural sealant, and a Merocel tampon. In concordance with our preferred method, the authors do not routinely use a lumbar drain and they reported a post-operative CSF leak rate of 0% in 59 patients with a high flow intraoperative CSF leak.

Post-operative CSF Leak: Risk Factors

Identification of patients at higher risk of post-operative CSF leak following EEA allows the surgeon to ensure particularly meticulous skull base reconstruction following tumor resection, as well as considering the pre-emptive insertion of a lumbar drain. A number of studies have been performed to identify

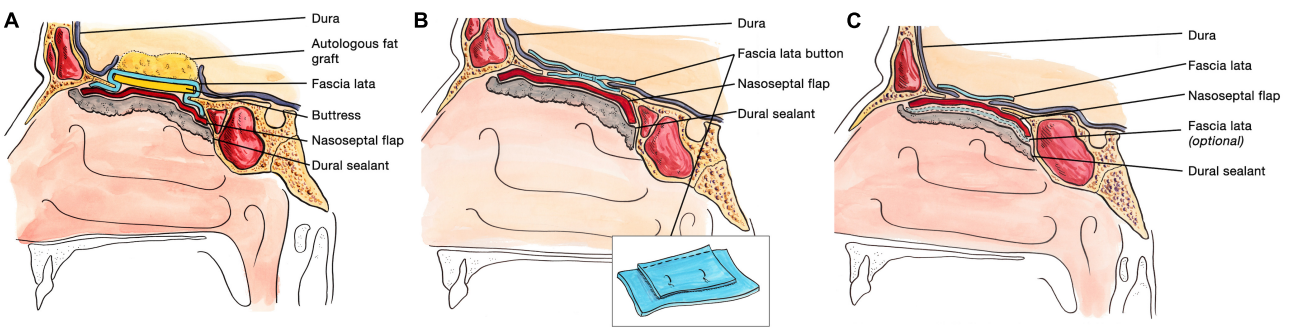

FIGURE 7 | Comparative sagittal view of the Gasket seal technique **(A)**, the Bilayer button technique **(B)**, and the Dublin technique **(C)** for skull base reconstruction following endoscopic endonasal resection of skull base tumors. **(A)** The Gasket seal closure technique consists of the placement of an autologous fat graft to eliminate dead space (this is not used when the 3rd ventricle has been opened), with a layer of fascia lata larger than the dural defect wedged in place with a solid buttress of bone or MEDPOR. This construct is then covered with a nasoseptal flap and secured with DuraSeal®. **(B)** In the bilayer button technique, two pieces of fascia lata are sutured together, with one much larger than the other. The larger piece of fascia lata is placed intradurally, and the smaller piece placed on the outside of the dural defect. This is then covered with a nasoseptal flap and secured with NasoPore and dural sealant. **(C)** In the Dublin technique, a fascia lata graft larger than the dural defect is placed intradurally as an inlay graft. This fascia lata graft is covered directly by a NSF, which may be secured with a further layer of fascia lata. Bioglue® is used to complete the skull base repair. Panel **(A)** adapted with permission from figure in Garcia-Navarro et al. (42). Panel **(B)** adapted with permission from figure in Luginbuhl et al. (43).

these risk factors, and BMI $\geq$ 30 has frequently been identified as being associated with an increased risk of post-operative CSF leak (31, 68, 69). The presence of an intra-operative CSF leak is strongly associated with a greater risk of post-operative CSF leak, as highlighted by the much higher rates of this complication in patients undergoing EEA compared to those having endoscopic *trans*-sphenoidal approaches to pituitary tumors (31).

There is also evidence to suggest that posterior fossa defects have a higher proclivity for post-operative CSF leak, which may not be surprising given their dependent location and the requirement for any vascularized nasoseptal flap to be transposed to a greater extent than if they were being used for an anterior fossa or sellar defect (69, 70). The rate of post-operative CSF leak has been shown to decrease as the experience of the operating surgeon increases, with data from our series of 270 endoscopic cases identifying a CSF leak rate of 21% in the first 90 cases, as compared to 1% in the last 90 cases (66).

CONCLUSION

Effective closure of the large osteodural defects created by EEA to skull base tumors is of vital importance in the prevention of post-operative CSF leak and meningitis. The addition of the NSF to multi-layered closure has been transformative in this regard, and as demonstrated in **Table 1**, has brought the risk of post-operative CSF leak below 5%. The role of routine, pre-emptive lumbar drain insertion requires further clarification but one randomized controlled trial has shown benefit in selected cases.

AUTHOR CONTRIBUTIONS

CH and MJ drafted and reviewed the manuscript. EK created the medical illustrations. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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METHODS
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Modified Maxillary-Swing Approach for Resection of Primary Malignancies in the Pterygopalatine Fossa

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Background: *En bloc* resection of malignancies in the pterygopalatine fossa (PPF) poses critical challenges. Using the modified maxillary-swing (MMS) approach, we achieved monobloc removal of primary malignancies in this region. This study provides a detailed account of the surgical techniques and indications used.

Methods: We enrolled seven patients with primary malignancies in the PPF during a period from January 2012 to January 2019 in this retrospective study. After malignancies were confirmed by biopsy as well as evaluation with computed tomography (CT) and magnetic resonance imaging (MRI) scans, all of the patients underwent MMS surgery under general anesthesia to extirpate these tumors. We performed regular postoperative follow-up using CT and MRI scans.

Results: *En bloc* resection was successfully performed in all cases. We observed negative margins in six cases and positive margins in one patient with adenoid cystic carcinoma, who received postoperative radiotherapy. The most common complication was facial numbness. During the follow-up period (range, 6–69 months), one patient suffered from recurrence, while the others did not.

Conclusion: The advantages of the MMS include a wide surgical field, full exposure, and easy manipulation. We expect this approach to become an alternative to the monobloc resection of malignancies in the PPF that involve the infratemporal fossa, maxillary sinus, nasal cavity, orbit, or oral cavity.

Keywords: malignant tumor, *en bloc*, modify, maxillary swing approach, pterygopalatine fossa

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INTRODUCTION

The pterygopalatine fossa (PPF) is a region marked by complex anatomy. Malignancies originating in this area pose a therapeutic challenge to surgeons due to its proximity to vital structures and limited exposure, making manipulation dangerous. Many surgical approaches have been designed to maximize exposure and minimize damage to the neurovasculature. Wei et al. first described the maxillary-swing approach for persistent or recurrent nasopharyngeal carcinoma in 1991 (1).

Sumi et al. (2) and Otremba et al. (3) later documented that this procedure also provided wide exposure of the PPF and facilitated proper clearance of lesions. However, they did not take into account the following two facts: (1) the posterior osteotomy behind the maxillary tubercle inevitably involves a close margin, sometimes even resulting in tumor rupture and spillage (2, 4) and (2) the surrounding canals and foramina (e.g., infraorbital fissure, sphenopalatine foramen, and greater palatine foramen and canal), which probably serve as sanctuary sites for tumor cells, are left undisturbed by conventional bony cuts (5). To overcome these problems, we introduced a modified maxillary-swing (MMS) approach for the monobloc resection of primary malignancies in the PPF.

METHOD

The modified procedure and the retrospective chart review were approved by the Independent Ethics Committee of Hunan Cancer Hospital, Changsha, China.

PATIENT DEMOGRAPHICS

From January 2012 to January 2019, seven patients who suffered from biopsy-confirmed primary malignancies in the PPF without any cervical or distant metastasis underwent MMS. This group included three male and four female participants, with a mean age of 46.3 years (range, 13–67 years). We routinely included computed tomography (CT) and magnetic resonance imaging (MRI) scans as well as laboratory tests in our preoperative assessments. Our decision as to whether to implement the MMS or another surgical procedure depended on the patient's written informed consent after surgeons had thoroughly explained the benefits and possible complications. Patients were excluded from this study for refusal or inability to tolerate curative surgery, the involvement of the retrostyloid space, or intracranial extension.

SURGICAL PROCEDURE

Patients underwent general anesthesia with nasotracheal intubation via the contralateral nostril. The patient was placed in the supine position. Ipsilateral tarsorrhaphy was routinely employed while the contralateral eye was covered. At the very beginning, through a 5-cm transverse incision along the dermatoglyph in the upper neck, we clamped the ipsilateral external carotid artery to reduce blood loss during the subsequent procedure. The surgical procedure started with a Weber–Ferguson incision that extended along the nasal contour to the medial canthus with a midline split of the upper lip to the base of the columella and then deviated to the infra-orbital lateral extension on the side to be exposed. The skin incision was deepened through the soft tissues and musculature until it reached the periosteum. The anterior soft tissue of the cheek was elevated minimally to expose the following underlying bony structure: the surface of the zygoma, the inferior orbital rim, and the frontal and alveolar processes of the maxilla. We made a palatal incision at midline and turned it laterally to the gums between the second premolar and the first molar. We used Wei's method, but with two technical modifications: (1) Coronal osteotomy was performed at the facial ridge and hard palate (HP), instead of at the hamulus of the pterygoid, to preserve the integrity of the posterior and posterolateral walls of the maxillary sinus (MS) and (2) parts of the maxilla, the orbital floor (OF) and infraorbital rim were swung simultaneously (**Figure 1**). At the zygomatic process, we inserted the oscillating saw through the MS in a horizontal position (along the transverse mucosal incision) to fracture the anterior maxilla and HP. Osteotomies were continued at the frontal process and the midline of the HP. We positioned a splitting chisel and drove it inward to the osteotomy line to separate the bony connection. The anterior maxilla could be retracted laterally with the facial skin, resulting in a broad view of the PPF (**Figures 2A,B**). We were then able to pay attention to the primary tumor. The medial pterygoid muscle was detached from the mandible, followed by transection of the lateral pterygoid muscle. We used the chisel to fracture the pterygoid process (PP). Finally, we removed the tumor in monobloc fashion together with the contiguous structures [the sinus posterior and posterolateral walls, the HP, the lateral wall of the nasal cavity (LWNC), and the PP and muscles]. As advocated by some experts (6, 7), we used a vascularized free flap to reconstruct such large defects (the lateral nasal wall, partial OF, and HP). The pedicle of the flap was tunneled through the subcutaneous soft tissue of the cheek to the neck for subsequent microvascular anastomosis. We then rotated the laterally swung maxilla back to its normal anatomic position and fixed it to the zygoma and the frontal and alveolar processes using miniplates and screws.

POSTOPERATIVE CARE

To decrease flap failure, we routinely performed postoperative monitoring of the free flaps every 2–3 h during week 1 postsurgery. Patients' noses were unilaterally packed with iodoform gauze for 5 days to keep the free flap in position. The use of postoperative antibiotics is recommended in the first 7 days.

FOLLOW-UP

We followed up with all patients every 3 months during the first 2 years, every 6 months during the next 3 years, and annually thereafter. Computed tomography, MRI, and positron-emission tomographic (PET) CT were used to detect any residual or recurrent disease if necessary.

RESULTS

All of the patients' demographic characteristics, tumor characteristics, pathological findings, and follow-up outcomes are summarized in **Table 1**. During surgery, we found that

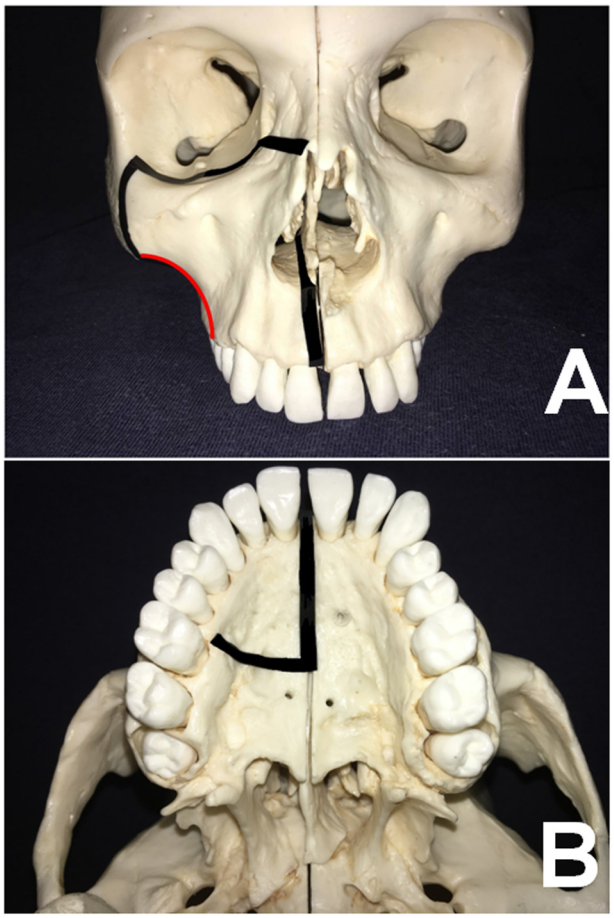

FIGURE 1 | (A,B) Based on the skull model, the osteotomy lines of the MMS approach are illustrated in the axial and coronal views, respectively. (The red arc indicates the osteotomy lines on the facial ridge).

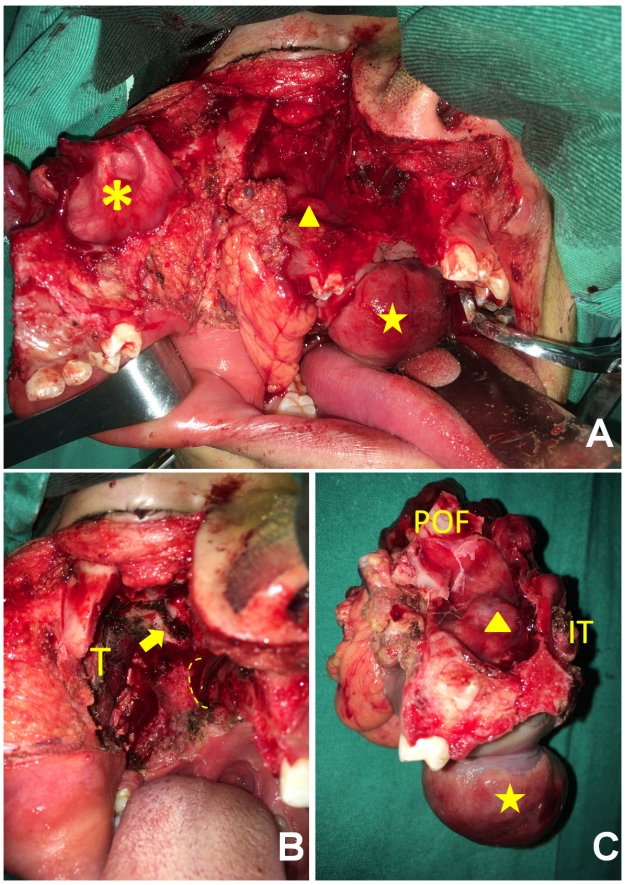

FIGURE 2 | (A) The anterior maxilla (asterisk) was rotated laterally, providing wide exposure to the tumor protruding into the sinus (triangle) and the oral cavity (star). **(B)** After tumor extirpation, the root of the pterygoid process (arrow), the choanae (dotted line), and the musculature of the infratemporal fossa were exhibited. T, temporalis. **(C)** The anterior view shows that the tumor had invaded the maxillary sinus (triangle) and the oral cavity (star). IT, inferior turbinate; POF, posterior orbital floor.

all of the neoplasms had irregular shapes, incomplete capsule or pseudocapsule, hard consistency, and good vascularization status. All of them had aggressively invaded neighboring bony structures such as the PP, the posterior and posterolateral walls of the maxillary antrum, the LWNC, and the HP (**Figures 2C**, **3A,B**). Mean operation time was 8 h (range, 6.5–10 h); the mean length of hospital stay was 10 days (range, 7–20 days). The mean amount of intraoperative bleeding was 200 ml (range, 100–400 ml). Gross monobloc resection was achieved in all cases, while negative microscopic margins were obtained in six. Because of the large bone and soft-tissue defects, all patients underwent immediate free-flap transfer reconstruction following tumor resection. In the current study, the workhorse flap was an anterolateral thigh flap for six patients and an anteromedial thigh flap for the remaining patient. One patient (case 3) with adenoid cystic carcinoma who showed microscopically involved surgical margins of the maxillary and infraorbital nerves was recommended to undergo postoperative radiotherapy at a moderate dose (66 Gy) within 6 weeks after discharge.

Regarding complications, all patients experienced expected postoperative facial numbness and epiphora. However, they exhibited varying degrees of relief within 6 months. Case 5 presented mild malocclusion postoperatively, but this deformity did not evolve into a functional disturbance during follow-up. Other morbidities, such as trismus, palatal fistula, facial paralysis, and diplopia, were absent in this cohort. The scars in the facial region are nearly invisible.

Patients widely complied with regular follow-ups. Postoperative imaging showed favorable outcomes for the reconstruction of soft-tissue defects and bone loss using the vascularized free flaps in the retromaxillary region (**Figures 3C,D**). The contents of the PPF and infratemporal fossa (ITF) were completely extirpated except for the lateral part of the ITF (**Figure 3D**). Of these seven patients, only one (case 5) showed recurrence in the ITF at the last follow-up visit and underwent surgical treatment at another tertiary hospital, while the other six are alive and disease-free.

TABLE 1 | Summary of demographics, tumor characteristics, pathological findings, and follow-up outcomes of all patients who underwent surgery using the MMS approach.

Case no.	Pathology	Age (years), sex	Presentation	Size, location and extensions	Follow-up	
					Months	Outcomes
1	Mucoepidermoid carcinoma	50, M	None	5 cm × 3 cm × 3 cm, right PPF and ITF, PP, HP	69	No recurrence
2	Mucoepidermoid carcinoma	67, F	Intermittent headache	6 cm × 5 cm × 4 cm, left PPF and ITF, IOF, PP, HP	54	No recurrence
3	Adenoid cystic carcinoma	45, F	Facial numbness	3 cm × 3 cm × 3 cm cm, left PPF and ITF, PP, LWNC	41	No recurrence
4	Myofibrosarcoma	59, F	Mild headache	4 cm × 4 cm × 3 cm cm, right PPF and ITF, IOF, OF, PP, LWNC, MS	25	No recurrence
5	Fibrosarcoma	13, M	Palatal protrusion and numbness	7 cm × 5 cm × 5 cm, right PPF and ITF, PR, HP, MS, OC	24	Local recurrence after 1-year follow-up, resected again, then no recurrence
6	Carcinoma in pleomorphic adenoma	40, M	Mouth angle Numbness and headache	4.5 cm × 4 cm × 3 cm, right PPF and ITF, IOF, OF, HP	16	No recurrence
7	Carcinosarcoma	50, F	Palatal protrusion and stuffy nose	3 cm × 3 cm × 3 cm, left PPF and ITF, HP, LWNC	6	No recurrence

HP, hard palate; ITF, infratemporal fossa; IOF, infraorbital fissure; LWNC, lateral wall of the nasal cavity; MS, maxillary sinus; OC, oral cavity; OF, orbital floor; PP, pterygoid process; PPF, pterygopalatine fossa.

DISCUSSION

The PPF is a relatively small and concealed area that communicates with intracranial and extracranial compartments via multiple bony canals and foramina through which different neoplasms can spread back and forth (5). The heterogeneity of the PPF's tissues makes it a bed for a wide spectrum of benign and malignant lesions with variable prognoses (8), but its anatomical complexity poses a challenge to surgeons who hesitantly commit to removing such lesions.

Several routes to the PPF have been explored. They are divided into three types: lateral, inferior, and anterior. The lateral approach, mainly referred to as the ITF approach, was pioneered, elaborated upon, and implemented by Fisch (9). It provides sufficient exposure to the PTF, the ITF, and the great vessels in the retrostyloid space, but it cannot offer good visualization of any tumor exceeding the midline. Additionally, this procedure requires mastoidectomy and transposition of the facial nerve, leading to postoperative conductive-hearing loss and neurological deficits. The inferior method, the so-called transmandibular approach, achieves only a wide view of the anterolateral compartment of the ITF and pterygoid hamulus. In addition, trismus and malocclusion hinder its widescale adoption. Anterior approaches, which include the transantral route, midface degloving, and lateral rhinotomy, create only a deep and narrow surgical field in the sinonasal cavity. Over the last two decades, great advances in nasoendoscopy have revolutionized patient care, and the application of the nasoendoscope has been promoted in the management of skull base tumors (10). Despite improving visualization, eliminating facial incision, and avoiding osteotomy, nasoendoscopic techniques, which are considered demanding procedures with steep learning curves, are usually associated with piecemeal resection. This compromises margin control and poses difficulties in managing intraoperative hemorrhage. Additionally, postoperative nasal morbidities such as nasal crusting, nasal obstruction, rhinorrhea, and an impaired sense of smell are not life-threatening but are objectionable and require long-term nasal care. Based on our review of the literature, only selected tumors with favorable histologies can be excised endoscopically (10–14).

Wei et al. first reported the maxillary-swing technique as an approach to persistent and recurrent tumors in and around the nasopharynx (1, 6). Otremba et al. have highly recommended adopting it to treat extensive ITF tumors, as it provides a broad view and poses minimal morbidity (3). However, most extensive tumors in this area protrude into the neighboring compartments at clinical onset. In addition, classic osteotomy protocol have the potential to corrupt the integrity of tumors, increasing the risk of tumor rupture, seeding, and consequent relapse. To overcome the pitfalls of the present method, we modified conventional osteotomies to achieve *en bloc* removal of such malignancies (**Figure 1**). First, the modified posterior osteotomy is initiated at the facial ridge and continued medially to the HP between the second premolar and the first molar. This bone cut is away from the primary site to avoid the risk of tumor rupture and protect the greater palatine artery during bone cutting in order to maintain a bloodless surgical field. Second, the anterior OF and infraorbital rim is rotated laterally, leaving *in situ* the posterior OF and infraorbital fissure, which are typically involved in tumors arising in the PPF due to their close topographical proximity.

After the partial maxilla is swung out, the remaining maxilla, the architecture of the sinonasal cavity and the OF can be seen under direct vision. According to Iannetti's and Friedman's theory (4, 15), the above-mentioned structures and the PP

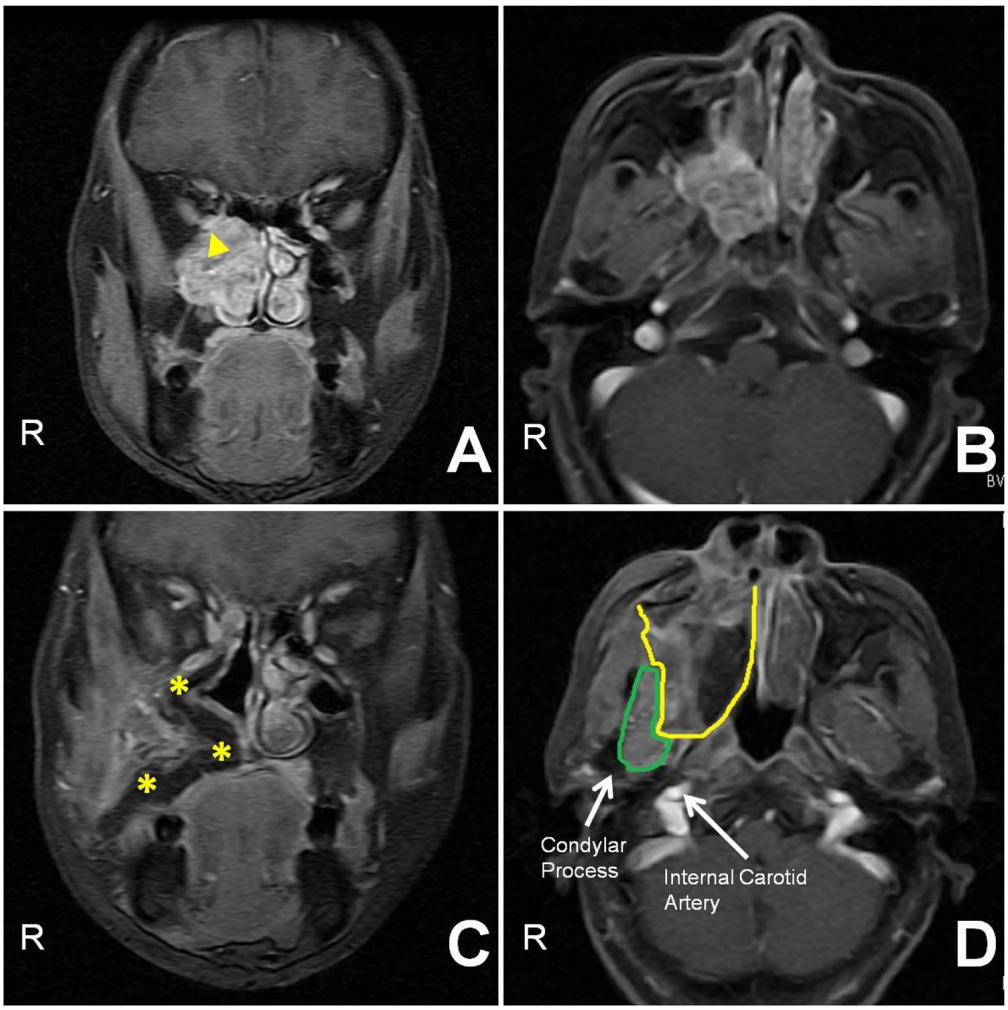

FIGURE 3 | (A,B) Preoperative contrast-enhanced coronal and axial T1-weighted MR images show that a tumor (triangle) occupied the PPF, invading the orbit and nasocavity. **(C)** Thirteen-month postoperative contrast-enhanced coronal T1-weighted MR image demonstrates that the flap (asterisk) supported the orbital contents and covered the defects without recurrence. **(D)** The postoperative contrast-enhanced axial T1-weighted MR image shows that the maxillary-swing approach failed to resect the lateral part of the infratemporal fossa (referred to as the "blind spot," bordered in green; the flap is encircled by the yellow line).

constitute the surgical planes of tumors in the PPF. The use of these boundaries can help surgeons define the physiological-cleavage planes to perform a truly oncological resection with adequate margins. However, we recommend removing them during surgical manipulation due to their inherent canals and foramina (e.g., sphenopalatine foramen, infraorbital fissure, and greater palatine foramen and canal), which probably serve as sanctuary sites for tumor cells (5). During tumor resection, brisk hemorrhage from the pterygoid plexus and internal maxillary artery is immediately encountered, and the surgical field is obscured by blood. In this circumstance, surgeons should take considerable caution to protect the internal carotid artery and eustachian tube from iatrogenic injury. These vital structures and the nearby condylar process are laterally located at the bottom of the surgical cavity created by the anterior approach. It should be noted that the maxillary-swing approach fails to resect the lateral part of the ITF, which is referred to as the "blind spot." It represents a three-dimensional area circled by the coracoid process, condyle, and internal carotid artery (**Figure 3D**) (7). If malignancies involve or are close to this region, the ITF approach or a combined method is documented as an alternative surgical technique in these cases (7). After tumor removal, bleeding can be easily controlled by pressure packing or suture ligation due to the wide exposure.

The 14% (1/7) rate of locoregional recurrence we encountered in our study is within average ranges, compared with the outcomes of other techniques described in the literature (4, 13, 14, 16, 17). The MMS procedure exhibits some competitive advantages over those other approaches: (1) improved visualization of the PPF, sinonasocavity and skull base, which boosts surgical safety, helps stop bleeding and facilitates subsequent reconstruction by a free flap; (2) highlighting the principles of *en bloc* resection and removal of inherent canals and foramina around the tumor, which potentially reduce local

recurrence; (3) preservation of the facial-nerve function and facial contours; and (4) minimizing postoperative trismus as the pterygoid muscle is resected. This modified procedure, however, has at least three drawbacks. First, the involvement of the "blind spot" impedes applications. Second, like the conventional way, the MMS causes cosmetic problems because of the incision in the upper lip. Third, there is a learning curve for undertaking this modified procedure.

Currently, summarizing the indications of the MMS approach would be premature due to the limited number of cases. Based on the analysis of the tumor characteristics we report in this study, there is a close correspondence between such abnormalities and the surrounding bony walls of the PPF, and all lumps extended to the ITF. Three of them protruded into the orbit via the infraorbital fissure, one extended to the oral cavity (OC) via the greater palatine foramen, two involved the MS, and three had eroded the lateral wall of the nose. This technique is therefore not only suitable for malignancies limited to the PPF but also for en bloc resection in cases of lesions that erupt into the ITF, MS, nasal cavity, orbit, or oral cavity, based on our preliminary practice. Under such circumstances, a rigorous preoperative evaluation of the disease with imaging studies should be conducted, and a multidisciplinary oncological institutional board should be assembled to seek consensus on the preferred treatment and surgical route, providing patients with the maximum benefit of expertise.

CONCLUSION

In summary, the MMS approach is noteworthy in that it provides access to the PPF. Based on our practice, this approach offers good exposure to this deep region, permitting monobloc resection of extensive malignancies therein involving the ITF, MS, nasal cavity, orbit, or OC, with acceptable surgical morbidities and oncological outcomes. Future studies are needed to validate the reproducibility and efficiency of the MMS technique across larger case series and longer follow-up periods.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article. The studies involving human participants were reviewed and approved by the Independent Ethics Committee of Hunan Cancer Hospital. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LX, WH, and JW contributed to the conception and design of the study. JW, YZ, JC, and XC contributed to the acquisition and analysis of the data. LX drafted the manuscript. All authors critically revised the manuscript, approved the final manuscript, and agreed to be accountable for all aspects of the works.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.530381/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Endoscopic, Endonasal Transsphenoidal Surgery for Tumors of the Sellar and Suprasellar Region: A Monocentric Historical Cohort Study of 369 Patients

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Background: The endoscopic endonasal transsphenoidal approach (EETA) is an established technique for the resection of a large variety of benign sellar and suprasellar lesions, mostly pituitary adenomas. It has clear advantages over the microscopic approach, like a superior close-up view of the relevant anatomy and the tumor-gland interface, an enlarged working angle, as well as an increased panoramic vision inside the surgical area. We have been performing the EETA for over a decade, and this study will focus on perioperative and postoperative outcomes and complications and their association with the learning curve.

Material and Methods: All patients in our tertiary referral center (n = 369) undergoing an EETA for a lesion of the sellar and suprasellar region between January 1st 2008 and December 31st 2018 were included, and data were retrospectively retrieved from the electronic patient records.

Results: Median follow-up after surgery was 55 months. Pituitary adenomas (n = 322) were the most frequent pathology. Headache (43.4%) and loss of vision (29.3%) were the most common presenting symptoms. Median procedure duration was significantly longer during the initial 5 years (106 *versus* 79 minutes; p <0.0001), but incidence of peri- and postoperative CSF leaks in the early years was not significantly higher. Knosp grade >2 was associated with perioperative CSF leak (p =0.002), and perioperative CSF leak was associated with postoperative CSF leak (p <0.001). Almost all cases of meningitis were preceded by a postoperative CSF leak. In 22.4% of patients, tumor

recurrence required additional therapy. Perioperative (iatrogenic) mortality was 0.8%. The overall hospital stay decreased over time from an average of 7 to 5 days, and the case load increased yearly (p =0.015).

Conclusion: The EETA is an excellent technique with complication rates comparable to or even lower than those in large microsurgical series in the literature. EETA has a significant learning curve affecting the procedure duration. Throughout the first 10 years following the transition from the microscopic approach to the EETA in our cohort, the caseload increased and hospital stay was reduced, while no increase in peri- and postoperative complications was observed.

Keywords: endoscopic endonasal surgery (EES), transsphenoidal approaches, pituitary tumor, cerebrospinal fluid (CSF) leak, pituitary adenoma

INTRODUCTION

Tumors with the highest incidence located in the sellar and suprasellar region are benign pituitary adenomas (1). They are derived from differentiated hormone-expressing cells located in the anterior part of the pituitary gland and are classified based on their size in microadenomas (<10 mm), macroadenomas (10–40 mm) or giant adenomas (>40 mm) or on their hormone-producing capacity (functional *versus* non-functional adenomas).

Functional adenomas (*e.g.* corticotropinomas, somatotropinomas, thyrotropinomas, and prolactinomas) generally arise from only one type of hormone-expressing cells and typically present as hypersecretory syndromes (*e.g.* Cushing's disease, acromegaly, hyperthyroidism, and hyperprolactinemia). Prolactinomas only require surgery when medical treatment is insufficient or not tolerated (2). Usually, gonadotropinomas do not lead to hypersecretory syndromes and are diagnosed similarly to the non-functional adenomas (3). Non-functional adenomas can originate from any differentiated hormone-expressing cell, but are generally diagnosed when symptoms occur due to the size of the tumor (4). This so called mass-effect can lead to headache, hypopituitarism and/or visual field deficits. These visual symptoms arise through compression following increasing size of the longitudinal axis and typically cause hemi-anopsia. Rarely, palsy of the 3rd, 4th, and/or 6th cranial nerves develops as a consequence of cavernous sinus invasion (5, 6). In very rare cases, pituitary apoplexy can occur which is characterized by sudden onset of severe headache and rapidly worsening visual field deficits or double vision caused by compression of nerves surrounding the gland. This is often followed by acute symptoms caused by lack of secretion of essential hormones. Additionally, incidentalomas in the pituitary region have become more frequent as the use of ever improving medical imaging techniques increased (7).

Less frequent benign pathologies in the sellar and suprasellar region are Rathke's cleft cysts and craniopharyngiomas. The former are embryological remnants of the Rathke pouch and only require surgical removal in case of mass-effect or progressive growth (8, 9). The latter are congenital tumors of the central nervous system, believed to arise from residual ectoblastic cells of the craniopharyngeal duct. Craniopharyngiomas are most often located above the pituitary gland and can be resected through the endoscopic endonasal transsphenoidal approach (EETA), but often require additional radiotherapy for optimal treatment (10, 11).

Other lesions of the sellar and suprasellar region that may need to be approached for biopsy or resection are meningiomas, gliomas, and germ cell tumors, although the EETA for these lesions is less widely applied.

Historically, the gold standard for surgical removal or biopsy of all of the above pathologies has been the microscopic transsphenoidal approach. Since the year 2000, skull base tumors have increasingly successfully been approached in an endoscopic way, and our team has been among the pioneers (12–15). The EETA has clear advantages, like the increased panoramic vision inside the surgical area, resulting in better orientation for the surgeons and better close-up view of the tumor–gland interface and the relevant anatomical landmarks (16–20). Typically, neurosurgeons and otorhinolaryngologists collaborate in these skull base approaches, where they combine their knowledge and expertise during the "two nostrils–four hands" surgery. However, EETA has its limitations as well, and there are some major drawbacks coming from a microscopic approach, mainly the loss of three-dimensional vision and the longer learning curve when the surgeon is unfamiliar with endoscopic procedures.

In our tertiary referral center we have been performing the EETA for lesions in the sellar region since April 2008, after a long period of using the microscopic approach. In this retrospective, monocentric cohort study we describe our 10 year experience with the EETA and evaluate the perioperative and postoperative outcomes, with emphasis on extent of tumor resection, cerebrospinal fluid (CSF) leakage, cranial nerve damage, recurrence, and the effects of the learning curve.

PATIENTS AND METHODS

Study Design and Data Collection

The study was approved by the Medical Ethical Committee of the University Hospitals Leuven (S63665).

Figure 1 depicts the flow diagram of the selection of potential patients in our electronic heath record system using two search

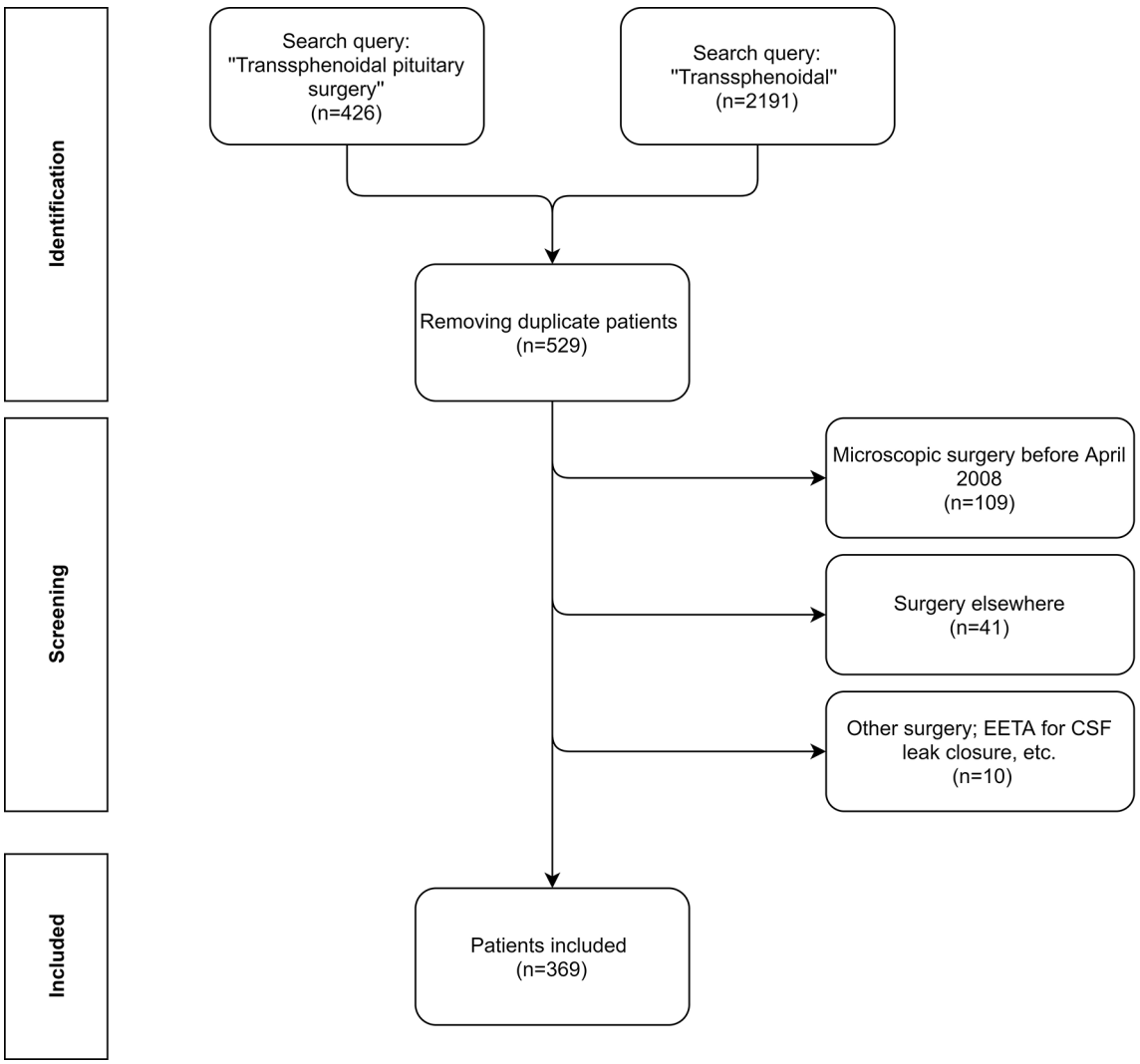

FIGURE 1 | Flow diagram of the patient inclusion process. The patients were initially identified using two search queries: ''Transsphenoidal pituitary surgery'' ''Transsphenoidal'' in 2 databases; 1 was the billing file, the other the medical records. Afterwards, all of the unique patients were screened for the inclusion criteria. Note that at our hospital we do not have a separate code for CSF leak closure. Finally 369 unique patients were included in this study.

queries between 2008 and 2018 (included). We did not include patients after 2018 to ensure a follow-up period of at least 1 year. Firstly, all patients who were billed for "Transsphenoidal pituitary surgery" (N = 426) were identified. Secondly all patients who had the word "Transsphenoidal" (N = 2191) mentioned anywhere in their electronic health record system were also identified. After removing the duplicates, 529 unique patients were found. We excluded patients that were operated *via* the microscopic approach (before April 2008), patients operated in other hospitals but in follow-up at our hospital, other types of surgery in the sellar/suprasellar region like closure of idiopathic/traumatic CSF leaks *via* a transsphenoidal approach and some other exceptions (see **Figure 1**). Subsequent removal of the patients who did not meet the inclusion criteria resulted in 369 unique patients. There was no age restriction. Patients who presented with a recurrence after surgery elsewhere or with a recurrence after previous microsurgical resection were also included.

The electronic health medical records were reviewed and analyzed for clinical, biochemical, and radiological data, procedure characteristics, perioperative complications, pathological examination of the tumor, postoperative outcomes, morbidities, and mortalities.

Patient Work-Up and Surgical Procedure

All patients were operated under general anesthesia by a team consisting of an experienced neurosurgeon and an otorhinolaryngologist. Our standard preoperative workup included a clinical and biochemical evaluation, an MRI of the sella, and a CT scan for neuronavigation (Brainlab ®, Munich, Germany). If visual impairment was suspected, an ophthalmological

examination was performed before surgery. All patients received perioperative antibiotic prophylaxis and a corticosteroid stress-dose. In all patients, a bilateral approach was used in three phases: the nasal, sphenoidal, and sellar phase.

After careful out-fracture of the inferior and middle turbinate with the Cottle, the natural ostium of the sphenoidal sinuses was reached *via* the paraseptal corridor (nasal phase). To enlarge the natural ostium of the sphenoidal sinuses, the inferior 3rd of the superior turbinate was removed by a monopolar cutting. The access was then enlarged by a mushroom punch and Kerrison rongeurs with caution not to damage the septal branch of the sphenopalatine artery (posterior septal artery) in patients where the use of a nasoseptal flap was anticipated. After finishing the bilateral sphenoidotomy, a posterior septectomy with resection of the rostrum and intersinus septum allowed a wide access to the face of the sella with optimal identification of the optico-carotic recess (OCR), carotic and optic protuberance on both sides, and the clival indentation (sphenoidal phase). At this point we start the two-nostril, four-handed technique to remove the sellar bone with a Kerrison punch or microdrill using a diamond burr, depending on the erosion of the bone, open the inner periosteum, and perform a meticulous endoscopy-guided resection of the tumor (sellar phase). For macro-adenoma, the inferior and lateral components of the tumor were resected before approaching the superior aspect to avoid limited vision after descent of the redundant diaphragm into the operative field. For micro-adenoma, the most challenging step was always identification of the right tumor-gland plane. In case of unclear identification, pathologic tissue which differs in color and consistency from normal pituitary tissue was removed until normal gland-tissue could be recognized.

In case of craniopharyngiomas, a resection of the solid part of the tumor and of the wall of the cystic component was attempted. In case of Rathke's cleft cysts, a broad opening of the cyst was performed to drain the contents, and a biopsy of the wall was taken.

In the absence of perioperative complications, Spongostan® (Ethicon, Edinburgh, Scotland) and Tisseel®(Baxter, Deerfield, Illinois, U.S.) were used to close the sellar defect. In case of a small (punctiform) intra-operative CSF-leak, a multilayer reconstruction using fascia and/or fat and a free mucosal graft in overlay were used. In case of large intra-operative CSF-leaks (macro-adenoma, malignancies), in cases in which the arachnoid was thinned out and herniated into the sella, and in case of postoperative CSF-leak, a more extensive, multilayer closure was warranted using a mucoperiosteal flap (nasoseptal/Hadad flap) in overlay instead of a free flap. Placement of lumbo-external drainage and postoperative nasal packing was not included in our standard of care but was only performed in indicated cases.

Statistical Analysis

All statistical analysis was performed using IBM SPSS Statistics 27® software or Microsoft Excel 2016. Categorical variables were expressed in frequencies and proportions. Normally distributed continuous variables were presented as means and their standard deviations, skewed continuous data as median and range. Normality was tested using Shapiro–Wilk test. Means were compared using Independent Samples T-test; medians were compared by non-parametric tests. Significance was set at $p < 0.05$. One-way ANOVA was performed to investigate the association between categorical and continuous variables when appropriate, otherwise a Kruskal–Wallis test was performed. Pearson Chi-Square test was used for the association between categorical variables. Kaplan–Meier curves were calculated, and log-rank tests were subsequently performed. Recurrence-free interval was defined as time in months from date of operation until moment of either hormone suppression therapy, additional surgery, radiotherapy, or last follow-up depending on which event takes place first. Overall survival interval was defined as time in months from date of operation until date of death or last follow-up.

RESULTS

Patient Characteristics

A total of 369 patients were analyzed (**Table 1**). More than half of the cohort (54.2%) was female, and the median age at surgery was 50 y (range 4–89). The median follow-up duration was 55.0 months.

TABLE 1 | General patient demographics.

Patient demographics			
Number of patients		***N* = 369**	**%**
Female		200	54.2
Median age—year		50.0	
	Range	4–89	
Median follow-up duration—months		55,0	
	Range	12–142	
Pathology			
Pituitary adenoma		322	**87.3**
	Non-hormone expressing adenoma	117	31.7
	Corticotroph adenoma	71	19.2
	Somatotroph adenoma	70	19.0
	Gonadotroph adenoma	21	5.7
	Lactotroph adenoma	14	3.8
	Thyrotroph adenoma	3	0.8
	Plurihormonal adenoma	26	7.0
Rathke cleft cyst		19	**5.1**
Craniopharyngioma		9	**2.4**
Other		19	**5.1**
Smoking		146	39.6
	Active	73	19.8
	Median pack–years	15,0	
	Range	1–200	
Comorbidities		263	71.3
	Cardiovascular	231	62.6
	Obesity	154	41.7
	Diabetes mellitus	56	15.2
	Renal	24	6.5
	Respiratory	17	4.6
	Multimorbidity	73	19.8

General demographics of the included patients.
Median pack–years are calculated for the active and non-active smokers. Cardiovascular comorbidities mainly include hypertension and hypercholesterolemia. Diabetes mellitus includes type I and type II. Renal comorbidities include chronic kidney disease and dialysis. Respiratory comorbidities include asthma, COPD, and interstitial lung diseases.
Bold values are used to highlight the main groups.

Obesity was a common comorbidity (in 67%) with 154 patients classified as overweight (25 ≤ BMI < 30), 66 as class I obesity (30 ≤ BMI < 35), 23 as class II obesity (35 ≤ BMI < 40), and four as class III obesity (BMI ≥ 40). Five patients were diagnosed with multiple endocrine neoplasia syndrome.

Forty-five patients (12%) in this cohort study presented with a recurrence after previous microsurgical resection.

Clinical and Biochemical Manifestations

Over half of the patient population presented with a non-hormonal mass effect (61.5%) (**Table 2**). Typical visual symptoms were diagnosed in 108 patients during ophthalmologic screening and included 90 patients with bitemporal hemianopsia, 15 patients with diplopia, and three with both symptoms. Eleven patients presented with pituitary apoplexy. Seventeen percent (35/201) of female patients presented with amenorrhea, and 30 patients reported sexual dysfunction. Fatigue was also a very common symptom in our cohort (151 patients).

Biochemical evaluation revealed that 52% of patients had a central deficiency in at least one hormonal axis (**Table 2**). Hormone excess in this surgical series involved mostly the somatotropic axis (82 patients), followed by the corticotropic axis (69 patients).

Tumor Characteristics and Histopathology

The most frequently encountered tumors were pituitary adenomas (87.3%), followed by Rathke 's cleft cyts (5.1%) and craniopharyngiomas (2.4%). Most of the pituitary adenomas were macroadenomas (231/322), followed by microadenomas (75/322) and giant adenomas (14/322) (**Figure 2A**). Tumor size was not known in two. Cavernous sinus invasion by pituitary adenomas was radiologically classified using the Knosp staging system (**Figure 2B**). Non-hormone expressing adenoma was the most frequent pathological diagnosis (31.7%), followed by corticotroph adenoma (19.2%) and somatotroph adenoma (19%) (**Table 1**). The plurihormonal adenomas were further classified according to their main hormone expression pattern, and the results are visualized in **Figure 2C**. Furthermore, the EETA was used in 19 less frequent pathologies: six meningiomas, two chordomas, two oncocytomas, two plasmacytomas, two cholesterol granulomas, one germinoma, one chondrosarcoma, one neurinoma, one post-radiation sarcoma, and one leiomyosarcoma.

TABLE 2 | Presurgical signs and biochemical evaluation.

Presurgical signs and symptoms and biochemical evaluation	All		Pituitary adenoma	
	N	%	N	%
Non-hormone mass effect	227	61.5	185	57.3
Headache	160	43.4	127	39.3
Typical visual field defect	108	29.3	83	25.8
Hypopituitarism	192	52.0	172	53.4
Partial pituitary insufficiency	65	17.6	59	18.3
Panhypopituitarism	72	19.5	58	18.0
Partial pituitary insufficiency + hormone excess	53	14.4	53	16.5
Panhypopituitarism + hyperfunction	2	0.5	2	0.6
Hormone excess	264	71.5	238	74.0
ACTH	65	17.3	65	20.2
TSH	4	0.8	3	0.9
GH	61	16.5	61	18.9
PRL	17	4.3	17	5.3
Disconnection hyperprolactinaemia	91	24.7	66	20.4
ACTH + Stalk effect	4	1.1	4	1.2
TSH + Stalk effect	1	0.3	1	0.3
Mixed GH + TSH	1	0.3	1	0.3
GH + Stalk effect	6	1.6	6	1.9
Mixed GH + PRL	14	3.8	14	4.3

Surgical Procedure and Perioperative Complications

Overall, we observed a progressive increase of EETA-procedures over the last decade (R^2 of 0.499; p =0.015) with a median yearly operated number of patients of 33 (range 15–43). Moreover, a significant reduction in operation time between the first 2 years of EETA [2008–2010: median 110.5 min, range (50; 710)] and the last three operation periods [2013–2014: median 79 min, range (40; 229); 2015–2016: median 95 min, range (20; 338); 2017–2018: median 80 min, range (20; 196)] ($p < 0.001$) could be observed (31.5; 15.5; 30.5 min respectively).

The most common perioperative complication was a CSF leak, with a significantly higher rate in the craniopharyngioma group than in the pituitary adenoma group ($p = 0.014$) (**Table 3**). There was no significant decrease in perioperative CSF leak rate over the years ($p = 0.999$). Knosp grade >2 was significantly associated with a higher perioperative CSF leak incidence ($p < 0.001$) in the pituitary adenoma group.

In two patients, profuse bleeding from the cavernous sinus impaired visualization resulting in an incomplete tumor resection.

Three patients suffered from a perioperative carotid artery hemorrhage. In only one patient, the bleeding could be controlled during the operation using Flo-Seal® (Baxter, Deerfield, Illinois, U.S). The other two patients required interventional radiological therapy, which was successful in one patient.

In general, a macroscopically complete resection was achieved in 78% of the patients.

Postoperative Complications

Median hospitalization duration was 6 days (range 1–62 days). Pairwise comparisons after Bonferroni correction showed that for operation period 2008–2010 (7 days, range 2–62), 2011–2012 (7 days, range 3–20) and 2013–2014 (6 days, range 2–59) the median hospitalization duration was significantly longer than for operation period 2017–2018 (5 days, range 1–17) ($p = 0.001$; $p < 0.001$; $p = 0.004$ respectively).

Transient and permanent diabetes insipidus were the most common postoperative complications (**Table 3**), followed by postoperative CSF leak and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Zooming in on postoperative CSF leak, 15 cases (4.0%) were diagnosed during the hospitalization period and 12 after hospital

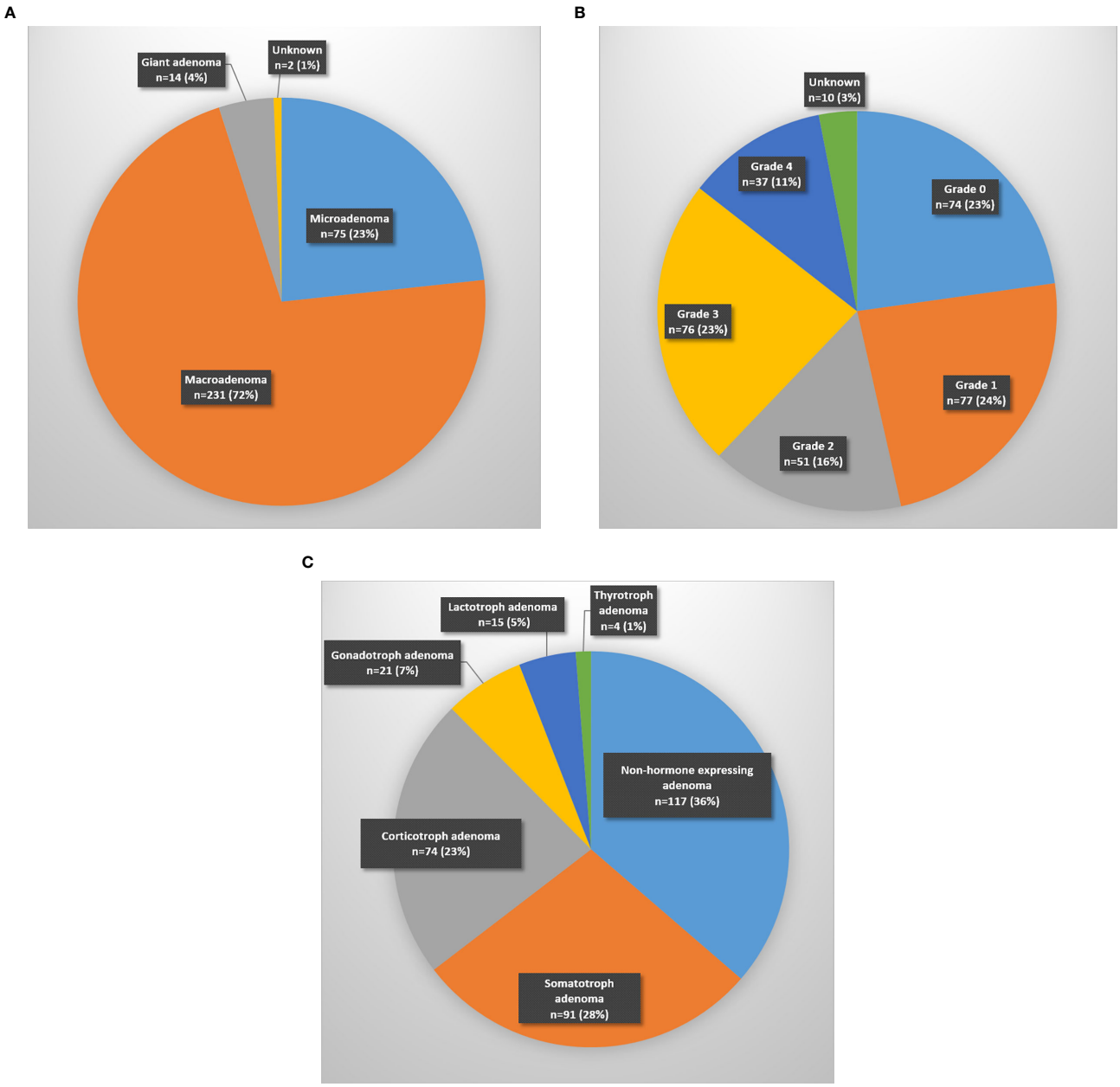

FIGURE 2 | Distribution of pituitary adenomas according to **(A)** size (micro < 10 mm; macro 10–40 mm; giant > 40 mm), **(B)** Knosp classification-grade, **(C)** main hormone expression pattern.

discharge (3.3%). Looking at factors that were potentially associated with postoperative CSF leak, surgical experience with EETA did not seem to play a role as no significant decrease was seen over the years (p = 0.0725). Far lateral extension (Knosp grade > 2) was also not associated with a higher incidence of postoperative CSF leak (p =0.875). We did see that the occurrence of perioperative CSF leak was associated with higher postoperative CSF leak incidence ($p < 0.001$). For the management of this complication, placement of a lumbo-external drainage (LED) alone was sufficient in seven patients; LED combined with surgical closure was needed in 16 patients. One patient required ventriculo-external drainage (VED) with surgical closure and another required ventriculo-peritoneal drainage (VPD) with surgical closure. One patient received only surgical closure without LED, and one patient refused a re-intervention and received only antibiotics. The average duration of temporary CSF drainage was 7 days (range 5–30 days). Surgical closure was always done by a multilayer

TABLE 3 | Perioperative and postoperative complications in relation to the pathology treated.

	All		Pituitary adenoma		Rathke cleft cyst		Craniopharyngioma		Other	
Median operation duration—minutes	88,0		88,5		66,0		114		92	
Range	20–710		25–338		40–126		59–229		20-710	
Perioperative complications	73	19.8%	59	18.3%	4	19%	6	66.7%	4	23.5%
Perioperative CSF-leakage	68	18.4%	55	17.1%	4	19%	5	55.6%	4	23.5%
Cavernous sinus hemorrhage	2	0.5%	2	0.6%	0	0.0%	0	0.0%	0	0.0%
Carotid artery hemorrhage	3	0.8%	2	0.6%	0	0.0%	1	11.1%	0	0.0%
Postoperative complications										
Postoperative CSF-leakage	27	7.3%	19	5.9%	5	23.8%	3	33.3%	0	0.0%
Diabetes insipidus										
Transient	42	11.4%	42	13.0%	0	0.0%	0	0.0%	0	0.0%
Permanent	37	10.0%	22	6.8%	9	42.9%	5	55.6%	1	5.9%
SIADH	17	4.6%	17	5.3%	0	0.0%	0	0.0%	0	0.0%
Infections	9	2.4%	6	1.9%	2	9.5%	1	11.1%	0	0.0%
Nasal obstruction	33	8.9%	26	8.1%	4	19%	0	0.0%	3	17.6
Cranial nerve damage	6	1.6%	5	1.6%	0	0.0%	0	0.0%	1	5.9%
Intracranial hemorrhage	3	0.8%	3	0.9%	0	0.0%	0	0.0%	0	0.0%
Intracranial hemorrhage and cerebral ischemia	1	0.3%	1	0.3%	0	0.0%	0	0.0%	0	0.0%
Cavernous sinus hemorrhage	1	0.3%	1	0.3%	0	0.0%	0	0.0%	0	0.0%

reconstruction using a graft with or without a free/pedicled mucoperiosteal flap in overlay. A free muscle graft was used in 11 cases, four patients received a nasoseptal flap (overlay) combined with a muscle graft (inlay). In two patients a fat graft was used and in one patient a fascia graft.

Meningitis (eight cases) was the most frequent postoperative infection; in all but one patient this was preceded by a CSF leak in the postoperative phase. One sellar abscess developed after resection of a non-hormone expressing adenoma.

A postoperative intracranial hemorrhage was observed in four patients. In two patients symptoms of (permanent) third cranial nerve damage (diplopia and ipsilateral mydriasis) lead to the diagnosis of intracranial hemorrhage resulting in localized brain stem or cerebral ischemia. One of these patients presented with a giant adenoma with extensive cavernous sinus invasion (Knosp grade 4). The other case was a recurrence with extensive suprasellar invasion. In the other two patients the intracranial hemorrhage was found following decreased consciousness, headache, and decreased visual acuity. In total, six patients had ophthalmological confirmed cranial nerve damage after surgery. In three patients the right third cranial nerve was permanently damaged. The other three patients had transient visual problems. A last complication was severe epistaxis requiring surgical intervention in two patients. No septal perforations were observed.

Recurrence and Overall Survival

At last follow-up, local control after EETA was 83.2% (**Table 4**). Focusing on the factors determining local control, previous surgical therapy and tumor size did not decrease the chance of local control (p =0.576, p = 0.462). Tumor regrowth requiring surgical reintervention was seen in 19.3% of patients with pituitary adenomas. The median time to additional surgical intervention was 15.3 months (range 1–96.5 months). Ultimately, 93.0% of patients had their tumor controlled either through additional surgery, radiotherapy, medication or a combination. **Table 4** displays recurrence rates and reintervention rates per disease category. In the pituitary adenoma group, most often additional therapy was needed for plurihormonal (34.6%), lactotroph (28.6%) and somatotroph (27.1%) adenomas. Corticotroph and gonadotroph adenomas had the lowest recurrence rates (16.9% and 14.3%), but with a high surgical reintervention rate (9.9% and

TABLE 4 | Recurrence rates and interventions in relation to the pathology treated.

Recurrence rate

		Total		Surgical reintervention		Other interventions*	
Pituitary adenoma		62	19.3%	24	7.5%	38	11.8%
	Non-hormone expressing adenoma	15	12.8%	8	6.8%	7	6.0%
	Corticotroph adenoma	12	16.9%	7	9.9%	5	7.0%
	Somatotroph adenoma	19	27.1%	4	5.7%	15	21.4%
	Gonadotroph adenoma	3	14.3%	2	9.5%	1	4.8%
	Lactotroph adenoma	4	28.6%	1	7.1%	3	21.4%
	Thyrotroph adenoma	0	0.0%	0	0.0%	0	0.0%
	Plurihormonal adenoma	9	34.6%	2	7.7%	7	26.9%
Rathke cleft cyst		3	17.6%	3	17.6%	0	0.0%
Craniopharyngioma		2	22.2%	1	11.1%	1	11.1%
Others		16	94%	9	53%	7	41.2%

*"Other interventions" are radiotherapy and hormonal suppression therapy.

9.5%) as there is often no hormonal suppression therapy for these tumors. **Figure 3A** shows the Kaplan–Meier recurrence-free interval curves for the three most frequent types of pathology. There was no significant difference between the groups in recurrence-free interval ($p > 0.76$). **Figure 3B** shows the Kaplan–Meier recurrence-free interval curves for the pituitary adenomas operated during the first 5 years in comparison to the last 5 years. There was no significant difference between the first 5 years and last 5 years ($p = 0.886$).

Overall, three patients died due to iatrogenic complications: one after a carotid artery hemorrhage, one due to a tonsillar herniation with a Chiari I malformation as predisposing factor, and one after an intracranial hemorrhage and unsuccessful rehabilitation.

DISCUSSION

In our large cohort of 369 patients that were operated by an EETA for a (para)sellar lesion between 2008 and 2018, demographics were very comparable to those of other large retrospective analyses of pituitary pathologies (1, 21). The incidence of pituitary adenomas is generally higher in females mainly due to a higher frequency and earlier signs of hyperprolactinemia in females (*e.g.* amenorrhea) (22). Not surprisingly, the majority of sellar and suprasellar lesions were pituitary adenomas (21).

Headache is a very common preoperative complaint of the patient, and our results are comparable to the literature, but unfortunately headache is also very common in the general population and therefore unspecific (23–25). Visual signs and more specifically, bitemporal hemianopsia are much more specific and also more common (28–100%) when there is pathology located at the (para)sellar region, according to the literature (26). Interestingly, the prevalence of visual signs in our cohort (29.3%) is located at the lower end of the reported incidence in the literature. This is unlikely to be due to smaller tumor size, as the incidence of macroadenomas in our cohort is roughly the same as in literature (27). A more plausible explanation is the fact that we only reported visual symptoms confirmed by an ophthalmologic examination.

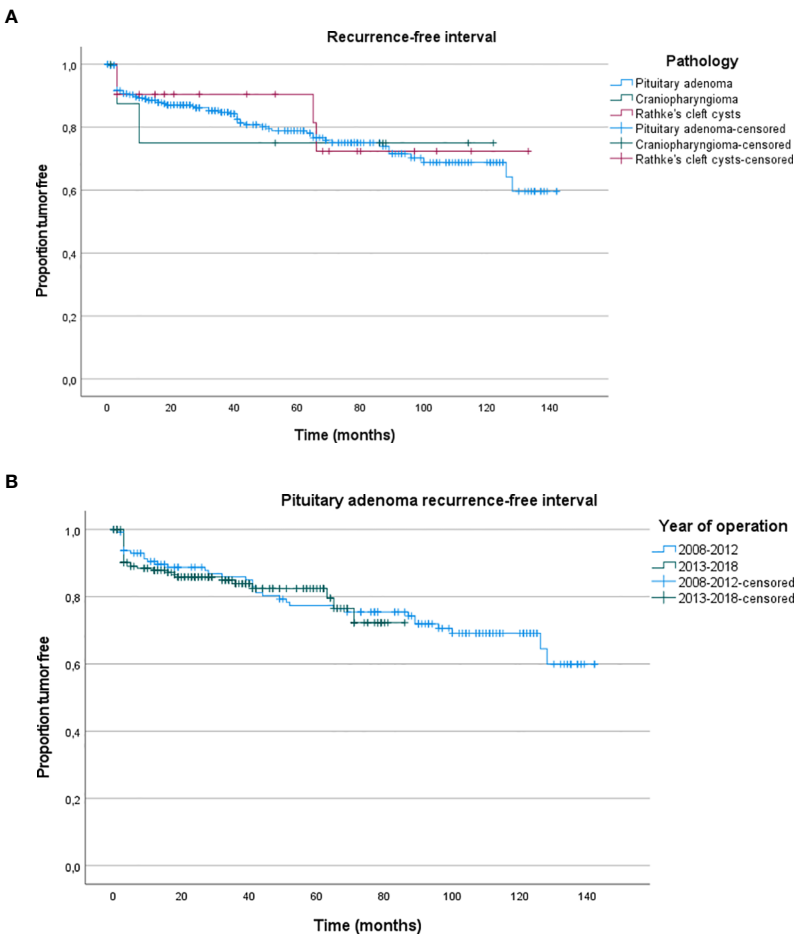

FIGURE 3 | **(A)** Kaplan–Meier recurrence-free interval curves for the three most frequent histological types. **(B)** Kaplan–Meier recurrence-free interval curves for the pituitary adenomas operated during the first 5 years in comparison to the last 5 years.

In our experience, there was a clear learning curve reflected in duration of the surgical procedure. The EETA-procedures were initially longer, and surgical time dropped significantly going from the first two years to years 3 and 4 and then further during years 5 and 6, to then stabilize. Other authors did not observe this reduction in operative procedure duration, attributing this phenomenon to an increase in familiarity with EETA paralleling a higher acceptance of more complicated cases (28, 29). Nonetheless, we also noted a clear increase in case load over time.

Overall, the EETA is a less traumatic route to the sella as previous studies have reported (19, 30). In our cohort we did not observe any iatrogenic septal perforation, and the prevalence of epistaxis was slightly lower than reported in other series (1.25–11%) (31–33).

Looking at the complications, our observed rate of perioperative CSF leak (18.4%) compares favorably to what other authors reported, with incidences ranging from 15 to 25% with even reports up to 60% (29, 34–37). Younus et al. reported a decrease in perioperative CSF leak (from 60 to 33%) when the surgeon gained more experience (38). We could not observe this trend in our cohort even after including our earliest cases. This can be explained by a meticulous surgical technique ahead from the very beginning. Knosp grade is used to determine the cavernous sinus invasion in order to see preoperatively if macroscopic total resection is feasible or not (39). We found that a Knosp grade >2 is associated with higher perioperative CSF leak. A higher Knosp grade is associated with a higher invasiveness and in order to achieve a macroscopic total resection, the surgeon is required to do more extended manipulations, resulting in an increased chance of damaging the arachnoid (40, 41). Patel et al. reported that cavernous sinus invasion was not associated with perioperative CSF-leak, but did not specify their definition of cavernous sinus invasion (42).

Postoperative CSF leakage is a frequent, serious, and costly complication resulting in a higher risk of meningitis and a longer hospital stay (43, 44). The cause of this complication is either lack of recognition of a perioperative CSF leak or an incomplete closure of the leak, but small perioperative CSF leaks are not always noticeable without enhanced visualization (45).

Our rate of postoperative CSF leakage is 7.3%. Other authors report rates ranging from 1.4 to 16.9% (46, 47). Not surprisingly, there are a vast number of studies investigating how to prevent this complication (36, 48, 49). Our study shows, not surprisingly, that a perioperative CSF leak is predictive for a postoperative leak, which has been suggested in the past (50, 51). More recent literature has shown that a more intensive therapy including a perioperative lumbar drain and nasoseptal flaps in high risk patients, like those undergoing revision surgery, could be beneficial (29, 36, 37, 52, 53).

The hospitalization duration has also significantly decreased over the years. However, our hospitalization is still slightly longer (median of 5 days) than in some recently published reports, describing short-hospital-stay protocols of 3 days or less. This is mainly due to the organization of patient care in our hospital, not to a higher frequency of postoperative morbidities (54, 55).

Recurrence in pituitary adenoma occurred in around 20% of cases, which is lower than previously reported in the literature, although strongly dependent on the tumor-characteristics (24, 49, 50).

According to a recent meta-analysis, the pooled surgical remission for acromegaly is 54.8%, which is lower than the 72.9% observed in our cohort (56).

For corticotroph adenoma, Braun et al. reported that the recurrence rate ranged from 1 to 41% depending on the study, but with an average rate of 14% which is in line with the recurrence rate of our corticotroph adenoma subgroup of 16.9% (**Table 4**) (57).

Both of these types of adenomas can recur either as a macroscopically visible adenoma or as a microscopic adenoma, even undetectable on imaging, but merely based on evolution of hormonal levels. In the former case, surgery can be repeated, but in the latter, medical therapy or radiation therapy is to be considered. Lactotroph adenomas are generally not treated by surgical intervention. Only after failed medical therapy or intolerance, surgery is considered. However, surgery is often insufficient to reach complete remission. Our results in lactotroph adenomas (71.4%) are comparable to those previously reported (58–60).

CONCLUSION

In this large historical cohort with long-term follow-up, EETA has proven to be a safe and efficient technique. Surgical teams that want to switch from a microscopic to an endoscopic approach should take into account the initial slightly longer operation time. However, in our series, already in the initial years, the caseload increased and hospital stay was reduced, while no increase in peri- and postoperative complications was observed. This series further adds to the body of evidence that EETA is the new gold standard for treating patients with (para) sellar lesions.

DATA AVAILABILITY STATEMENT

The data in this study are available upon reasonable request to the corresponding author. Requests to access these datasets should be directed to vincent.vanderpoorten@uzleuven.be.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical Committee of the University Hospitals Leuven (S63665). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LG and ZQ: conception, data collection, drafting the article, and revising the article for important intellectual content. AS: initial data collection and revising the article for important intellectual content. MJ, JM, JLo, SV, JLa, and MB: revising the article for important intellectual content. VV: conception, data collection, drafting the article, and revising the article for important intellectual content. All authors contributed to the article and approved the submitted version.

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Lipidomics Identified Lyso-Phosphatidylcholine and Phosphatidylethanolamine as Potential Biomarkers for Diagnosis of Laryngeal Cancer

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Background: Laryngeal cancer (LaC) remains one of the most common tumors of the respiratory tract with higher incidence in men than in women. The larynx is a small but vital organ on the neck. The dysfunction of the larynx can cause serious health problems such as hoarseness, respiratory distress, and dysphonia. Many lipids (e.g. phospholipid, cholesterol, fatty acid) have been recognized as a crucial role in tumorigenesis. However, the lipid biomarkers are lacking and the lipid molecular pathogenesis of LaC is still unclear.

Methods: This study aims to identify new LaC-related lipid biomarkers used for the diagnosis or early diagnosis of LaC and to uncover their molecular characteristics. Thus, we conducted serum and tissue nontargeted lipidomics study from LaC patients (n = 29) and normal controls (NC) (n = 36) *via* ultra-high performance liquid chromatography (UHPLC) coupled with high resolution mass spectrometry (HRMS). Multivariate and univariate statistics analyses were used to discriminate LaC patients from NC.

Results: As expected, a lipid panel including LPC (16:0) and PE (18:0p_20:4) was defined to distinguish the LaC patients from healthy individuals with very high diagnosis performance (area under the curve (AUC) value = 1.000, sensitivity value = 1.000, and specificity value = 1.000). In addition, the levels of Cer, CerG1, SM, PC, PC-O, PE, PI, PS, and ChE in the LaC group significantly increased as compared with the NC group. However, the levels of LPC, LPC-O, LPE, LPE-p, and DG in the LaC group significantly deceased when the one was compared with the NC group. Among significantly changed lipid species, lysophospholipids containing a palmitoyl chain or an arachidonic acid acyl chain remarkably decreased and phospholipids including a palmitoyl chain or an arachidonic acid acyl chain increased in the LaC patients.

Conclusion: Our results not only indicate that lipidomics is powerful tool to explore abnormal lipid metabolism for the laC, but suggest that lysophospholipids and phospholipids may serve as potential biomarkers for diagnosis of LaC.

Keywords: laryngeal cancer, lipidomics, UHPLC-mass spectrometry, biomarker, lipid metabolic abnormality

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INTRODUCTION

Laryngeal cancer is the most common head and neck cancer, causing heavy health care and economic burdens. Currently, the Global Burden of Disease Cancer Collaboration estimated the prevalence of LaC to be 21.1%, with a male to female ratio of 5:1, and approximately 10% of patients in metastatic or end-stage (1). Notably, over the past 30 years, the burden of this malignancy (expressed in years lived with disability) has increased by nearly 25% (2).

Some LaC patients have been diagnosed at the advanced stage and have an unsatisfactory treatment effect (3). Early detection of LaC is essential for treating this disease. Although some imaging methods, for example computed tomography (CT) (4), positron emission tomography (PET) scan (5), and magnetic resonance imaging (MRI) (6), are commonly used in the screening and detection of LaC, current imaging methods are challenged by problems related to availability of primary healthcare workers capable of assessing images. Thus, there is still an urgent need to identify novel biomarkers for LaC screening or detection.

Lipidomics, focusing on comprehensive profiling of lipids in complex biological matrice, is a powerful tool to identify disease-related lipid biomarkers contributing to diagnosis of disease, and to explore disordered lipid metabolism in the development of diseases. It has been widely applied in many studies, such as diabetes (7, 8), lung cancer (9), liver cancer (10, 11), oral cancer (12) and so on. Serum biomarkers related to head and neck cancer was explored by Yonezawa et al. (13), and they revealed that the levels of several metabolites associated with glycolytic pathways significantly increased in patients with head and neck cancer. However, the levels of several amino acids (e.g., serine, methionine, valine, and thyroxine) were too low. Plasma lipidomics was performed and revealed tamoxifen-induced alteration of the hepatic lipid profile and its association with the lipid profile (14). AA-containing PCs might have potential utility as novel and predictive biomarkers for tamoxifen-induced hepatic steatosis and phospholipidosis. Unfortunately, no laryngeal cancer-associate lipidomic study has yet been performed.

The aims of this study are to identify reliable serum biomarkers in diagnosing LaC and early-stage LaC, and to comprehensively elucidate the abnormal lipid metabolism related to the onset and development of LaC utilizing nontargeted lipidomics method based on UHPLC/Q-TOF mass spectrometry. Thus, a total of 65 participants were enrolled to discover a novel lipid panel and test its diagnosis performance, and to explore abnormal lipid metabolism pathways related to LaC (**Figure 1**).

Abbreviations: LaC, laryngeal cancer; NC, normal control; MTBE, tert-butyl methyl ether; ACN, d acetonitrile; MeOH, methanol; IPA, isopropanol; PL, glycerophospholipid; AA, arachidonic acid; UHPLC, ultra-high performance liquid chromatography; HRMS, high resolution mass spectrometry; QC, quality control; RSD, relative standard deviation; FA, fatty acid; OAHFA, (O-acyl)-1-hydroxy fatty acid; Cer, ceramide; CerG1, glucosylceramide; CerG2, galactosylceramide; SM, sphingomyelin; LPC, lyso-glycerophosphatidylcholine; LPC-O, LPC with alkyl substituents; PC, glycerophosphatidylcholine; PC-O, PC with alkyl and alkenyl substituents; LPE, lyso-glycerophosphatidylethanolamine; LPE-p, LPE with alkenyl substituents; PE, glycerophosphatidylethanolamine; PE-p, PE with alkenyl substituents; PI, glycerophosphatidylinositol; PG, glycerophosphatidylglycerol; PS, glycerophosphatidylserine; SL, sphingolipid; ChE, cholesterol ester; DG, diacylglycerol; TG, triacylglycerol; PLS-DA, partial least squares-discrimination analysis; LysoPL, lyso-glycerophospholipid; PUFA, polyunsaturated FA.

MATERIALS AND METHODS

Clinical Samples

Serum samples collected from 29 patients diagnosed with laryngeal cancer (LaC) and a set of 36 sex-age matched normal controls (NC) were from the Second Hospital of Dalian Medical University (Dalian, China) during the period 2018 to 2020. These subjects were in the age range of 53–80 years. Among these LaC serum samples, 15 cases were in the early stage of laryngeal cancer, i.e. T1NOMO stage. The LaC serum samples were collected before surgical resection and then stored at −80°C until lipidomics analysis. Eighteen LaC tissue (LaCT) and 16 adjacent noncancerous tissue (ANT) samples were also provided by the Second Hospital of Dalian Medical University (Dalian, China). Among these LaC tissue samples; 11 cases were in T1NOMO stage. This research was approved by the Second Hospital of Dalian Medical University Institutional Ethics Review Board, and all participants provided written informed consent.

Total Lipid Extraction

Serum samples taken out of the −80° refrigerator were thawed and homogenized by vortex. A total of 300 μl of cold methanol (HPLC-grade, Merck, Darmstadt, Germany) including seven lipid internal standards (i.e., FFA (16-d3), LPC (19:0), Cer (d18:1/17:0), SM (d18:1/12:0), PC (19:0/19:0), PE (17:0/17:0), TG (15:0/15:0/15:0)), purchased from Avanti Polar Lipids (Alabaster, USA), was added into 40 μl of each serum sample, followed by a 30-s vortex. Then, 1 ml of HPLC-grade tert-butyl methyl ether (MTBE) was added and the mixture was homogenized for 10 min. After that, 300 μl of ultrapure water (Milli-Q system, Millipore, Billerica, MA) was added. Next, the mixture was vortexed and centrifuged (4°C, 14,000*g*) until to form the two-phase system. About 400 μl aliquot of the upper layer were drawn and dried in a vacuum centrifuge and then stored at −80°C prior to LC-MS analysis. Quality control (QC) samples were made by mixing equal aliquots from each serum sample and pretreated using the same procedures as that description of the real samples. The QC sample was inserted into the batch after every six real samples to assess the reproducibility of the preparation and the LC–MS system.

Tissue sample were weighed. About 400 μl of cold methanol including seven lipid internal standards was added, followed by the homogenization at 25 Hz for 2 min on a mixer mill MM400 (Retsch, Haan, Germany). And then 1 ml of MTBE was added and the mixture was vibrated for 15 min. After that, 300 μl of ultrapure water was added. The mixture was vortexed and centrifuged (4°C, 14,000*g*) until to form the two-phase system. About 200 μl aliquot of the upper layer were drawn and dried in a vacuum centrifuge and then stored at −80 °C before LC–MS

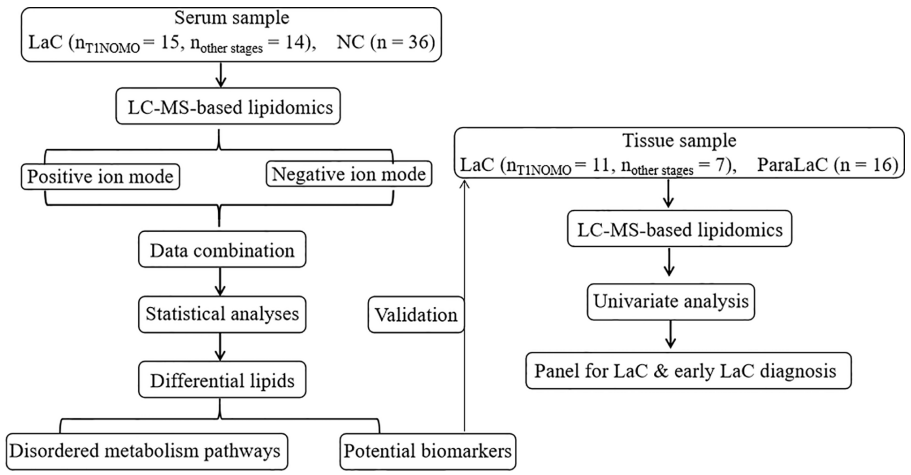

FIGURE 1 | Flowchart of the study design.

profiling. Details on lipid internal standards that were added to samples before lipidome extraction are summarized in **Table S1**.

Lipidomics Analysis

The lipidome was analyzed using Waters ACQUITY UPLC (Waters, Milford, USA) coupled with a Triple TOF 5600 Plus mass spectrometer (AB SCIEX, USA) system. Before LC–MS analysis, the lyophilized samples were reconstituted in the mixed solution including CH_2Cl_2 and MeOH (2:1 v/v) and then diluted in the ACN-MeOH-H_2O solution (65:30:5 v/v/v). Next, 5 µl of the diluted sample was separated on the C8 ACQUITYTM column (100 × 2.1 mm, 1.7 µm), (Waters, Milford, MA, USA). The column temperature was kept 60°C. The elution rate was set 0.3 ml/min. The mobile phase A was ACN:H2O (6:4 v/v) and the mobile phase B, was IPA: ACN (9:1 v/v), both containing 10 mM ammonium acetate. The initial elution gradient began with 50% B, kept for 1.5 min, followed by a linear increase to 85% B at 9.0 min, then reached at 100% B within 0.1 min, and maintained for 1.9 min. Lastly, it returned to 50% B within 0.1 min and held for 1.9 min to equilibrate column. The scanned m/z range of MS signal was 200–1,250 Dalton in both positive and negative ion modes. The capillary voltages of the positive and negative ion modes were set at 5.5 and −4.5 kV respectively. The interface heater temperature was set at 500 and 550°C for positive and negative ion modes, respectively.

Identification of Lipids

The structural compositions (e.g. PC18:0_20:4) of lipids were identified when characteristic ions and fatty acyl fragments appeared in the MS/MS spectrum. For those without fatty acyl fragments but with only characteristic ionic information, they would be annotated with total no. of carbon atoms and double bonds of acyl chains, e.g., PC36:0. Furthermore, for lipids that could not produce MS/MS fragments, extraction ion chromatogram (EIC) was performed based on an in-house lipid database for these lipids with a mass tolerance of 10 ppm to obtain the observed m/z and t_R. And then, these lipid candidates were further confirmed by comparing the relative t_R between the known lipids and the candidate peaks within a given lipid class.

Data Processing and Statistical Analysis

The lipids were identified according to previous published paper (15). The detected lipids were quantified *via* MultiQuant™ 2.1 (AB SCIEX, Concord, Canada) software with a mass error of ±0.05 Da and t_R shift of ±0.25 min. Lipidomics data were normalized by the corresponding internal standards.

The supervised partial least-squares discriminant analysis (PLS-DA) was performed on SIMCA-P software (13.0 version, Umetrics Umeå, Sweden), in Pareto scaling mode, which suppresses noise interference *via* dividing each variable by the square root of the standard deviation. Nonparametric test in Wilcoxon, Mann–Whitney test mode, was implemented to identify significantly altered lipids (p <0.01 & FDR <0.05) by the comparisons between the LaC and NC groups and heatmap was produced by the open-source software MultiExperiment Viewer (MeV, version 4.9.0). Receiver operating characteristic (ROC) curves of a binary logistic regression using SPSS software version 19 (SPSS, Inc.) were performed. The bar graph of the significantly differential lipid (sub)classes was drawn on the GraphPad Prism software (6.0 version).

RESULTS

Clinical Characteristics of the Laryngeal Cancer Patients and the Normal Controls

The detailed clinical information of the LaC and NC groups are provided in **Table 1**. Laryngeal cancer staging was performed in 29 patients who underwent laryngeal cancer resection according to the 8th edition of the AJCC Cancer Staging Manual (16). In this study, T1NOMO stage of laryngeal was also considered for

TABLE 1 | Characteristics of the subjects for lipidomics analyses.

Characteristics	Serum sample		Tissue sample	
	LaC	NC	LaC	ParaLaC
No.	29	36	18	16
Sex (male/female)	29/0	36/0	18/0	16/0
Age (years)	61.56 ± 8.96	56.22 ± 16.07[–a]	64.59 ± 9.58	62.08 ± 8.05
BMI (kg/m^2)	24.01 ± 3.71		24.30 ± 3.06	24.84 ± 2.74
FPG (mmol/L)	5.64 ± 0.87	5.71 ± 0.91	5.78 ± 0.97	5.70 ± 1.09
TB (μmol/L)	13.65 ± 4.64	16.21 ± 7.10	13.63 ± 4.12	13.87 ± 6.51
HCT (%)	43.48 ± 3.48	43.92 ± 4.15	43.85 ± 4.05	44.48 ± 2.59
HGB (g/L)	146.36 ± 13.22	148.54 ± 13.85	147.47 ± 16.06	150.50 ± 10.52
MCHC (g/L)	336.44 ± 10.23	338.11 ± 6.58	335.82 ± 10.39	338.17 ± 11.03
MCH (pg)	31.14 ± 2.43	31.64 ± 1.27	31.64 ± 1.82	31.84 ± 1.61
MCV (fL)	92.54 ± 6.27	93.48 ± 3.91	94.22 ± 4.86	94.15 ± 3.87
PLT (10^9/L)	223.92 ± 56.60	215.23 ± 65.20	213.29 ± 43.17	220.92 ± 34.78
WBC (10^9/L)	6.66 ± 1.66	7.33 ± 1.88	6.56 ± 1.28	6.77 ± 1.26
RBC (10^{12}/L)	4.72 ± 0.50	4.69 ± 0.41	4.60 ± 0.55	4.71 ± 0.33
Urea (mmol/L)	6.09 ± 1.74	5.86 ± 2.09	6.89 ± 2.01	6.51 ± 1.78
UricAcid (μmol/L)	381.20 ± 82.41	360.34 ± 83.75	391.88 ± 84.75	405.41 ± 99.99

[a]*NC group lacks of BMI information. Data represent mean ± SD.*

diagnosing the disease at an early stage. The age and sex between the LaC group and the NC group are matched as much as possible.

Lipidome Fingerprinting Between Patients With LaC and the NC

Lipidomics profiling was performed for comparative analyses of the serum samples collected from the LaC patients (n = 29) and the NC subjects (n = 36). The total ion current chromatograms of serum were shown in (**Figure S1**) for LaC and NC subjects in both positive and negative ion modes, respectively. In this study, 390 lipids were identified by exact mass-to-charge ratio (M/Z), retention time (t_R), and/or characteristic fragments. And the list of exact m/z values and retention times and characteristic fragments of all the lipid species identified was provided in **Table S2**. Among these identified lipids, 17 common lipid (sub)classes, mainly containing FA, LPC, LPE, PC, PE, Cer, SM, DG, and TG, were identified (**Figures S2A, B**). The QC sample was inserted into the analytical batch after six real samples to monitor the lipidomics data quality. In **Figure S2C**, relative standard deviations (RSD) of 47 and 87% of the detected lipids in all serum QC samples were less than 10 and 20%, respectively. The percentage of the identified lipids with RSD below 30% reached at 98%, which confirmed the analytical stability of the LC-MS-based lipidomics method used to acquire the lipidome data. And the detected lipids with RSD less than 30% were used for the follow-up statistical analysis.

A supervised PLS-DA model was made based on those identified lipids from serum samples to explore whether abnormalities in lipid metabolism occurred during the development of laryngeal cancer. In **Figure 2A**, we could find that the LaC group was apparently distinguished from the NC group. Subsequently, 200 times of permutations were operated to evaluate whether the PLS-DA model is over-fitting. In **Figure 2B**, R^2 = (0.0, 0.359) and Q^2 = (0.0, −0.456) shown that this model is stable. These results implied that substantial lipidome alternations occurred underlying the onset and development of LaC. Sixty-two lipids with variable importance for the projection (VIP) >1.0 were recognized as key variables that contribute to the classifications.

Defining of Potential Lipid Biomarkers for LaC

At present, the identification of novel serum markers for diagnosing LaC remains a vital task, especially for the early detection of LaC (17). In the present study, we employed the nontargeted lipidomics method, identifying as many lipids as possible, to screen biomarkers.

To explore significantly differential lipid species between the LaC group and the NC group, a univariate analysis (non-parameter test) was performed based on the lipidomics data from the LaC and NC groups. The levels of 204 lipids were noted significant changes between the LaC patients and the NCs (p value <0.01 and false discovery rate (FDR) value <0.05). The information of the differential lipids are provided in **Table S3**. Finally, 43 of these lipids exhibited p <0.01, FDR <0.05 and VIP >1.0 in the two comparisons (**Figure 2C**). In addition, heatmap visualization based on 43 differential lipids was performed to obtain an overview of the pattern of lipidomic alterations with the LaC development in a clinical setting (**Figure 2D**). Subsequently, for these 43 potential lipid biomarkers, the best model was constructed by a binary logistic regression analysis with an optimized algorithm of the forward stepwise (Wald). At last, the combination of LPC (16:0) (**Figures 3A, B**) and PE (18:0p_20:4) (**Figures 3C, D**) was defined as the ideal lipid panel in distinguishing patients with LaC from normal controls.

This lipid panel had high diagnostic performances, such as AUC value = 1.000, sensitivity value = 1.000, and specificity value = 1.000 in the discrimination of LaC from NC in the serum sample, respectively (**Figure 4A**). Furthermore, the serum lipid panel had a perfect performance in identifying the LaC_{T1NOMO} at

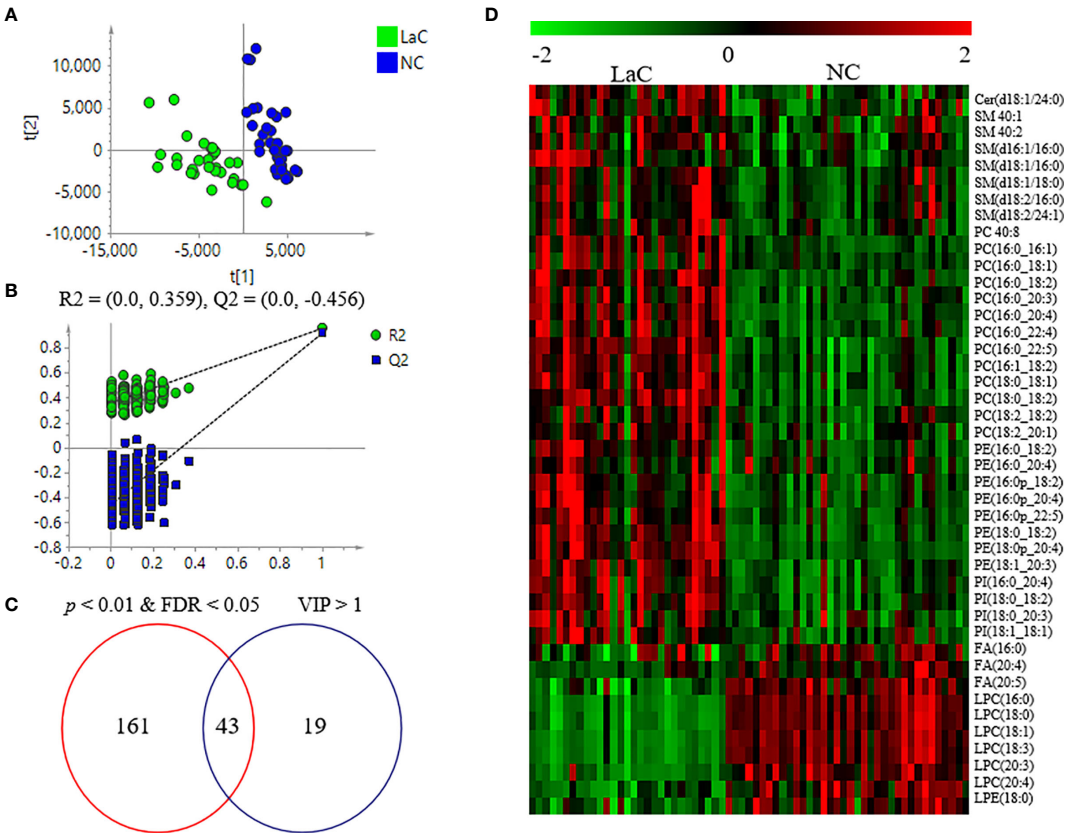

FIGURE 2 | **(A)** Score plots of PLS-DA between LaC and NC for lipidomics data from serum samples. **(B)** Cross validation of PLS-DA model between LaC and NC for lipidomics analyses. **(C)** Venn diagram shows the differential lipids between the LaC group and the NC group in serum samples. **(D)** Heatmap overview of the 43 differential lipids in distinguishing patients with LaC from the normal controls.

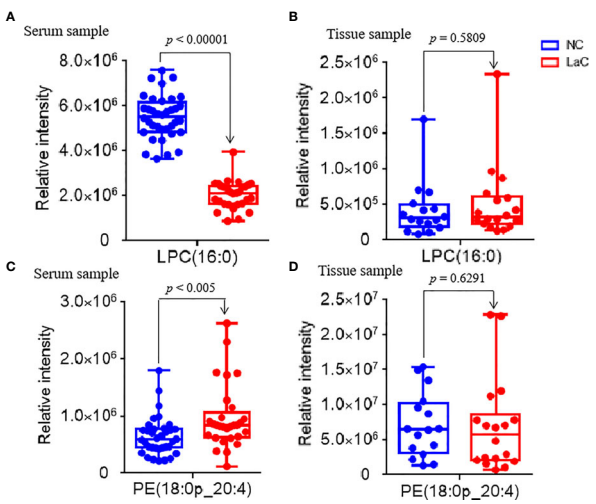

FIGURE 3 | **(A, C)** Serum relative intensity of defined potential biomarkers of LPC(16:0) and PE(18:0p_20:4), respectively. **(B, D)** Tissue relative intensity of defined potential biomarkers of LPC(16:0) and PE(18:0p_20:4), respectively.

early-stage LaC from the NC group, such as AUC, sensitivity, and specificity values of 1.000, 1.000, and 1.000, respectively (**Figure 4B**). Collectively, the serum lipid panel separated LaC from the NC with very high performance. Moreover, this lipid panel effectively discriminated patients with LaC_{T1NOMO} from the NC, highlighting the early diagnostic potential of this lipid biomarker pane.

Characteristics of Lipid (Sub)Classes Between the LaC and NC Groups

Lipid analysis between the LaC and NC groups was further investigated at the level of a given lipid (sub)class. For this purpose, the total content of all lipid species within a given (sub) class was compared between the LaC and NC groups according to Student T- test (p <0.05). The results shown that the relative contents of Cer, CerG1, SM, PC, PC-O, PE, PI, PS, and ChE in the LaC group significantly accumulated relative to the NC group. The levels of LPC, LPC-O, LPE, LPE-p, and DG in the LaC group significantly deceased when the one was compared with the NC group (**Table 2**).

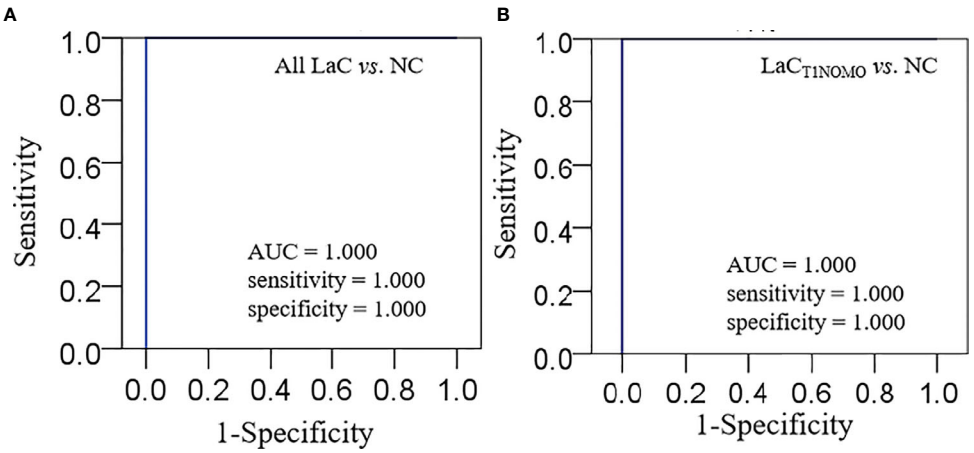

FIGURE 4 | **(A)** Characterization of ROC curve of lipid panel in the serum samples from the LaC group and NC group. **(B)** Characterization of ROC curve of lipid panel in the serum samples from the LaC_{T1NOMO} group and NC group. AUC, Area under curve; Lipid panel, LPC(16:0) and PE(18:0p_20:4).

TABLE 2 | Fold changes and *p* values of each lipid class between patients with LaC and controls.

Lipid class	Serum sample (LaC vs NC)		Tissue sample (LaCT vs ANT)	
	Fold change	*p* value	Fold change	*p* value
FA	0.95	5.0E–01	1.33	4.9E–01
OAHFA	1.04	8.0E–01	1.50	5.7E–01
Cer	1.15	3.2E–02	1.27	2.6E–01
CerG1	1.28	5.3E–04	1.16	5.4E–01
CerG2	1.06	4.7E–01	0.88	7.3E–01
SM	1.35	2.1E–06	1.17	2.5E–01
LPC	0.42	1.2E–22	1.37	3.1E–01
LPC-O	0.29	3.3E–26	1.65	1.3E–01
LPE	0.84	2.1E–02	1.09	7.5E–01
LPE-p	0.26	5.0E–15	1.48	3.5E–01
PC	1.84	2.9E–11	1.15	3.2E–01
PC-O	1.53	1.1E–06	1.12	5.0E–01
PE	1.69	1.1E–04	1.06	8.2E–01
PE-p	1.30	7.9E–02	1.11	6.3E–01
PI	1.66	5.2E–06	5.72	1.1E–01
PS	1.35	1.2E–06	3.25	1.6E–01
DG	0.47	4.4E–08	2.00	2.0E–01
TG	1.09	5.6E–01	0.27	1.4E–01
ChE	1.18	7.0E–03	1.51	2.3E–01

Another finding of interest was that the levels of large amount of PLs (e.g., PC, PE, and PI) with an arachidonic acid acyl chain and/or a palmitoyl chain significantly increased in LaC vs NC, and the levels of LPCs with an arachidonic acid acyl chain and/or a palmitoyl chain significantly decreased in LaC vs NC (**Figure 5**).

DISCUSSION

In this study, there were no significant differences in most clinical characteristics (**Table 1**) between the LaC and NC groups. Clinical outcomes clearly do not explain the observable phenotypic differences. Lipids are vital in cellular functions due to they are the essential components of the membrane structure, key regulators in signal transduction and energy storage (18). Abnormal lipid metabolism is growingly recognized as a hallmark of tumors and associated with the onset and development of many human diseases (19). Therefore, we performed a comprehensive lipidome analysis of larynx tumor between patients with LaC and the normal controls. As far as we know, a systematic evaluation of tumor lipid metabolism in LaC patients was reported for the first time.

The relative levels of most Cer and SM lipids significantly increased in the LaC patients when they were compared with the healthy controls. Ceramide is bioactive lipids of the sphingolipid pathway and play essential roles in cell signaling. Ceramide has been shown to be involved in stress-related cellular responses and apoptosis (20, 21). The imbalance of ceramide metabolism will greatly influence the physical and chemical properties of cells, leading to cellular dysfunctions. Many studies reported that ceramide metabolism altered in numerous cancers characterized by an increase of the Cer profile in cancer cells and tumor tissue (10, 22, 23). We speculated that the significant elevation in the level of the Cers in LaC patients could have resulted from the upregulated expression of the enzymes related to the synthesis of ceramide. It was reported that ceramide synthase in a salvage pathway was highly activated in several different tumors, such as human colon cancer (24), human non-small-cell lung cancer (25). *In vivo*, Cer can be also generated by the hydrolysis of SM through the actions of sphingomyelinases. Modulation of endogenous Cer levels is considered as a new therapeutic target for anti-cancer intervention strategies (26). In all, we hypotheses that reducing Cer biosynthesis or preventing from converting SM to Cer could inhibit LaC progression.

It is well known that PL is one of the most important components of a mammalian membrane bilayer. PC is the

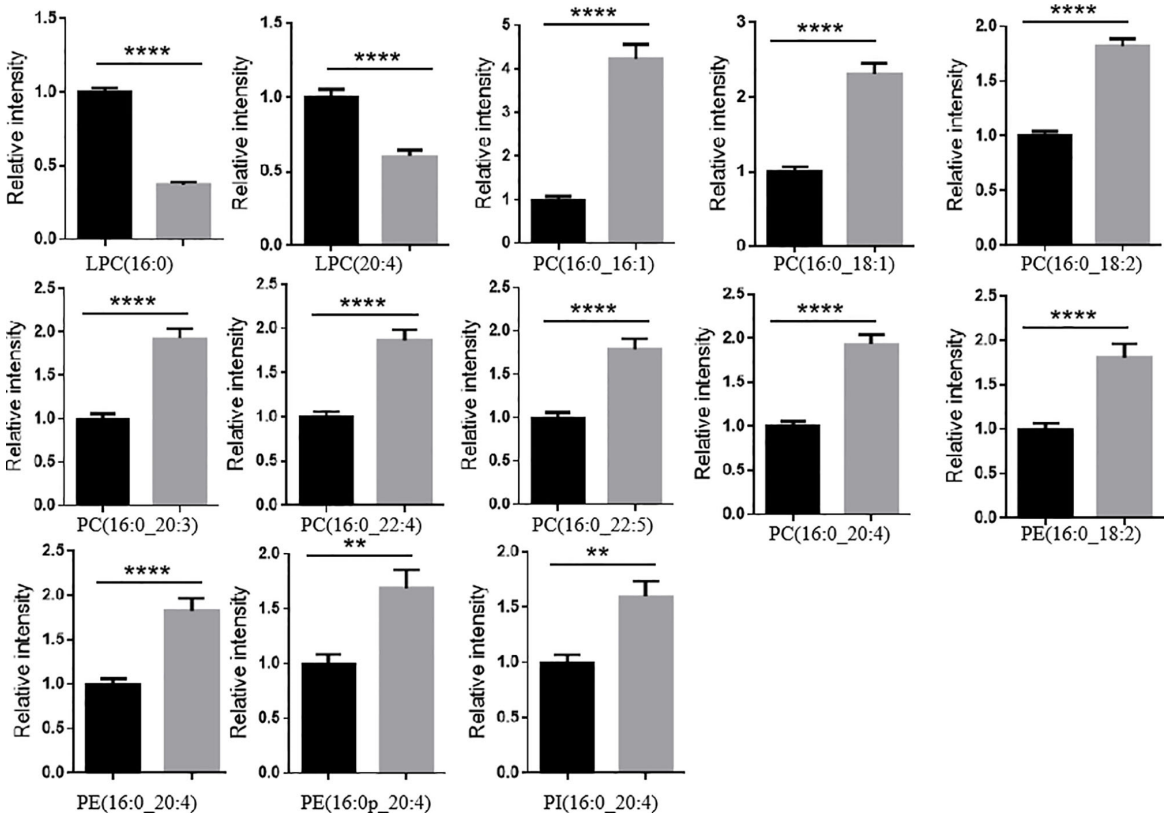

FIGURE 5 | LPLs containing a palmitoyl chain or an arachidonic acid acyl chain significantly decreased and PLs containing a palmitoyl chain or an arachidonic acid acyl chain mostly significantly increased in LaC vs. NC in serum samples. ****$p < 0.00001$, **$p < 0.001$.

mostly predominant component of PLs for biological membrane. Some reports have shown that PC metabolism is altered in the onset and development of many cancers, characterized by an elevation of PC (27–29). We deduced that the significant increase in PC may be due to an imbalance between PC and PE. Increased PC and an imbalance between PC and PE have been reported to be associated with obesity and NAFLD (30, 31), both of which are also associated with LaC occurrence. In addition, PC and LPC mutually convert, upregulating PC level which may come from LPC conversion. This point can be supported by the significant decrease in the level of LPC for LaC patients. Altogether, disordered PC lipid metabolism is closely associated with the development of Lac.

In this study, we also found that PLs with PUFA, in particular arachidonic acid residues, significantly increased in LaC patients. Arachidonic acid is one of major PUFAs in mammals. Long-chain acyl-coenzyme A synthetase 4 (ACSL4), shows preferential use of AA as its substrate and plays a role in the remodeling of AA-containing glycerolphospholipids by binding free AA. In consideration of significant increase of AA-residue-enriched PLs (e.g., PC(16:0_20:4), PE(16:0_20:4), PE(16:0p_20:4), PE (18:0p_20:4), PI(16:0_20:4), etc.), and the level of AA, so-called FA (20:4) significantly decreased in LaC serum, we speculated that ACSL4 may be activated and thereby prompt PLs accumulation, which associated with a greater degree of carcinogenesis in LaC tumor cells characterized by very abundant mitochondria. Of course, further investigation should be performed to explore our findings.

In summary, using nontargeted lipidomics method based on UHPLC-HRMS, we successfully identified a lipid panel [including LPC(16:0) and PE(18:0p_20:4)] that can effectively diagnose LaC from their cohort of healthy controls. Similar, this lipid panel shows ultrahigh performance in detection of the early-stage LaC from the healthy volunteers. To our best knowledge, this study provides the first evidence of a systematic alteration in lipid composition between LaC and NC groups. Cer, SM, and AA-enriched PLs showing close association with LaC, may be potential biomarkers and become potential targets for LaC. Out of consideration for the given small sample size, and to ensure the plausibility of our study results, further studies based on large-scale clinical samples and on the expression of related lipid enzymes will be required.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and

accession number(s) can be found below: https://www.ebi.ac.uk/metabolights/MTBLS2683.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Second Hospital of Dalian Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and BY conceived and designed the project. BY collected the clinical samples, performed the experiments, and analyzed the data. BY and JW wrote and improved the manuscript. JW and BY are responsible for the integrity and accuracy of the data in the research. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.646779/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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The Effect of Prolonged Duration of Intensity Modulated Radiotherapy for Nasopharyngeal Carcinoma

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Purpose: Radiotherapy is the most important primary treatment for patients with nasopharyngeal carcinoma. Generally, the treatment duration of radiotherapy takes six or six and half weeks with 30 to 33 fractions. The current study was conducted to evaluate the association between prognosis and the duration of radiotherapy in nasopharyngeal carcinoma patients.

Methods: Patients with primary nasopharyngeal carcinoma who were treated with intensity-modulated radiotherapy and concurrent cisplatin-based chemotherapy, with or without induction chemotherapy between January, 2008 and December, 2013 at a single institution were retrospectively reviewed.

Results: In total, 1292 patients were included. At a median follow-up of 71.0 months (range 2.0–126.0 months), locoregional recurrence, distant failure and death were observed in 8.8%, 12.2% and 15.6% of all patients, respectively. Estimated 5-year locoregional relapse–free survival, distant metastasis–free survival, progression-free survival and overall survival in patients with radiation ≤ 7 weeks versus patients with radiation >7 weeks were: 93.2% versus 87.0% ($P < 0.001$), 89.4% versus 84.4% ($P = 0.016$), 79.8% versus 70.6% ($P < 0.001$) and 87.2% versus 78.4% ($P < 0.001$), respectively.

Conclusions: Prolonged duration of radiotherapy with a significantly higher risk of distant metastasis and death in nasopharyngeal carcinoma patients. Understanding this point, healthcare providers should make efforts to avoid prolonged duration of radiotherapy to minimize the risk of treatment failure.

Keywords: nasopharyngeal carcinoma, intensity-modulated radiotherapy, prognosis, radiation, chemotherapy, duration

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BACKGROUND

Nasopharyngeal carcinoma (NPC) is endemic in Southeast Asia, including Southern China. The current management of locoregionally advanced NPC is radiotherapy combined with cisplatin-based concurrent chemoradiotherapy. Radiotherapy still plays the most important role in the treatment of NPC. Intensity-modulated radiotherapy (IMRT), which can deliver high doses to the target while

sparing adjacent tissues and organs, is now the mainstream radiation technique (1). With the development of imaging and modern radiation therapy techniques, the treatment outcomes have greatly improved in recent decades (2). Although NPC is highly sensitive to radiotherapy, a high failure rate is still noted in patients with advanced disease. There are some reasons for the high rate of failure. Advanced locoregional status is one of the most important factors (2, 3), and there are other factors, such as waiting time and radiation time, that could be managed (4).

Some studies have demonstrated that the treatment delay of radiotherapy was significantly associated with poorer survival rates in early stage head and neck cancer patients. Chen et al. also reported that a prolonged interval > 30 days between induction chemotherapy and radiotherapy was associated with a significantly higher risk of distant metastasis and death in NPC patients (5, 6). There are also some studies about the duration expansion of radiotherapy caused by different reasons. Studies have focused on the duration of radiotherapy and found that it is also an important factor that could affect treatment outcomes (4, 7). Therefore, it is important for health staff to be aware of the effects of radiation duration in clinical practice (6).

Induction chemotherapy has been demonstrated to effectively decrease the distant metastasis rate and improve survival (8, 9). Concurrent chemoradiotherapy (CCRT) has also indicated successfully decrease locoregional control, and now induction chemotherapy plus CCRT is recommended by National Comprehensive Cancer Network (NCCN) guidelines and has been practiced by clinical doctors (10). Although chemotherapy could bring benefits to patients, it also has side effects that could be a negative factor for the treatment outcome. Some reports also mentioned that the addition of concurrent chemotherapy also caused an increase in side effects, which is a common cause of the interruption of radiation, leading to a prolonged duration of radiation (4, 11).

The outbreak of COVID-19 is also associated with delay in treatment and loss of chances in terms of cancer treatment. Due to COVID-19, many cancer patients were affected for postponement of chemotherapy, radiotherapy and/or surgery, limited access to supportive care.

We hypothesized that a longer duration of radiotherapy (exceeding the normal span) would be correlated with worse survival in NPC patients treated with IMRT. Therefore, we conducted this retrospective study to assess the prognostic effect of the prolonged duration of radiotherapy in patients with NPC.

METHODS

Ethical Consideration

The Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center (SYSUCC) approved this retrospective review.

Patients

We retrospectively reviewed the inpatient medical records of 1292 newly pathologically confirmed primary nasopharyngeal carcinoma patients without distant metastasis treated with IMRT at SYSUCC between January 2008 and December 2013. Patients who received cisplatin-based concurrent chemotherapy were included, while those who did not receive concurrent chemotherapy or those who received concurrent chemotherapy that was not cisplatin-based were excluded.

Pretreatment Evaluation

All patients underwent complete physical examination, endoscopy, magnetic resonance imaging (MRI) of the head and neck, chest radiography, abdominal ultrasound, whole-body bone scanning, single photon emission computed tomography (SPECT) and dental assessment. Positron emission tomography and computed tomography.

(PET/CT) was performed when necessary. All the included patients were restaged according to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system.

Radiation

All patients received IMRT. The primary nasopharyngeal gross tumor volume (GTVnx) and the involved cervical lymph nodes were determined based on the MRI/CT and/or PET/CT imaging, clinical, and endoscopic findings. Enlarged retropharyngeal nodes together with primary gross tumor volume (GTV) were outlined as the GTVnx on the IMRT plans. The clinical tumor volume (CTV) represents the primary tumor with potential subclinical disease. The first clinical tumor volume (CTV1) was defined as the GTV plus a 0.5-1.0 cm margin (0.2 to 0.3 margin posteriorly) to encompass the high-risk sites of microscopic extension and the whole nasopharynx. Clinical target volume 2 (CTV2) was defined as the CTV1 plus a 0.5-1.0 cm margin (0.2 to 0.3 margin posteriorly) to encompass the low-risk sites of microscopic extension, the level of the lymph node, and the elective neck area (bilateral levels IIa, IIb, III, and Va were routinely covered for all N0 patients, whereas ipsilateral levels IV and Vb or supraclavicular fossae were also included for N1-3 patients). The prescribed dose was 66–70 Gy to the planning target volume (PTV), 60 Gy to PTV1, 54 Gy to PTV2, and 60–66 Gy to PTV of the involved cervical lymph nodes in 28 to 33 fractions. All patients were treated once daily, with five fractions weekly. Dose constraints to the critical structures were within the tolerance according to the RTOG 0225 protocol, and efforts were made to meet the criteria as closely as possible.

Chemotherapy

During the study period, concurrent chemoradiotherapy (CCRT) ± induction chemotherapy (IC) for stage II to IV disease was recommended according to our institutional guidelines. One of the following three regimens of IC were used: PF (80-100 mg/m2 cisplatin on day 1 and 800 mg/m2/d fluorouracil civ on days 1–5), TP (75 mg/m2 docetaxel on day 1 and 75 mg/m2 cisplatin on day 1) and TPF (75 mg/m2 docetaxel on day 1, 75 mg/m2 cisplatin on day 1 and 800 mg/m2/d fluorouracil civ on days 1– 5); all regimens were repeated every 3 weeks for 2–3 cycles. The study-defined concurrent chemoradiotherapy regimen was 80–100 mg/m2 cisplatin on day 1 every 3 weeks for 2–3 cycles or 30 mg/m2 cisplatin weekly. Patients receiving other chemotherapy regimens or who received only one cycle of induction or concurrent chemotherapy were excluded from this study. Adjuvant chemotherapy was less often

chosen because of poor compliance. Reasons for deviating from the institutional guidelines included organ dysfunction suggesting intolerance to chemotherapy, patient refusal, and the discretion of the doctors in individual cases.

Anti-EGFR Therapy Delivery

Both nimotuzumab and cetuximab were not recommended for NPC patients by the guidelines at that time. Therefore, the use of anti-EGFR therapy was determined by the patients' willingness and the experience of doctors. Intravenous nimotuzumab was administered at an initial dose of 200 mg weekly during the whole radiation period. Intravenous cetuximab was administered at an initial dose of 400 mg/m2 followed by 250 mg/m2 weekly throughout RT.

Duration of Radiotherapy

The duration of radiotherapy was calculated from the start of radiotherapy to the end of radiotherapy. All patients received radiotherapy in 28 to 33 fractions. We used a cut-off point of more than 7 weeks to define a longer duration of radiotherapy.

Follow-Up

Patient follow-up was measured from the first day of therapy to the day of the last examination or death. The patients were examined at least every 3 months during the first 2 years, with follow-up examinations every 6 months for 3 years or until death. The last follow-up date was 20 April 2019. Overall survival (OS) was calculated from day 1 after the completion of treatment to the last examination or death. Distant metastasis–free survival (DMFS) and locoregional relapse–free survival (LRRFS) were calculated from day 1 after the completion of treatment to first distant metastasis and locoregional relapse, respectively; progression–free survival (PFS) was calculated from day 1 after the completion of treatment to locoregional relapse, distant relapse or tumor-related death, whichever occurred first.

Statistical Analysis

The clinicopathological characteristics of the participants were assessed, and the differences in these characteristics were compared by $\chi 2$ test for categorical variables and t-test for continuous variables. Logistic regression analysis was used to identify confounders between the treatment groups. LRRFS, DMFS, PFS and OS were calculated using the Kaplan-Meier method. The differences in LRRFS, DMFS, PFS and OS between the two groups were tested using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. All statistical analyses were performed using SPSS 21.0 statistical software (Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 1292 NPC patients who were treated with IMRT between January 2008 and December 2013 at SYSUCC were analyzed in this study.

Among the 1292 patients, 290 were female and 1002 were male. The mean age at the time of reirradiation was 43.5 years (SD=10.2) for radiation duration ≤ 7 weeks and 45.8 years (SD=10.6) for radiation duration >7 weeks. All 1292 patients received cisplatin-based concurrent chemotherapy, and 647 patients received two or three courses of induction chemotherapy. 883 patients received radiotherapy within a duration less than 7 weeks, and 409 patients within a duration more than 7 weeks. Of the 409 patients, 253 (61.9%) patients experienced a relative long duration because of long-term public holidays (May Day holidays, National Days and Spring Festival holiday). The characteristics of the patients are shown in **Table 1**.

At a median follow-up of 71.0 months (range 2.0–126.0 months), the 1-, 3-, and 5-year follow-up rates were 99.2%, 97.8% and 91.2%, respectively. At the time of the analysis, 114 (8.8%) patients had locoregional failure, 157 (12.2%) developed distant metastases, and 202 (15.6%) died.

Patient Characteristics and Association With the Duration of Radiotherapy

The patient characteristics for the entire included cohort are displayed in **Table 1**. Patients with a duration of more than 7 weeks tended to receive anti-EGFR ($P < 0.001$). We also found that patients with a duration of more than 7 weeks were more likely to have advanced T stages ($P = 0.023$). However, after we

TABLE 1 | Characteristics of the 1292 patients.

Characteristics	Duration of radiotherapy ≤ 7 weeks (883 patients)	Duration of radiotherapy > 7 weeks (409 patients)	P-value
Age (years)	43.5±10.2	45.8±10.0	0.684
Sex			0.753
Female	196 (22.2%)	94 (23.0%)	
Male	687 (77.8%)	315 (77.0%)	
T category			0.023
T1	56 (6.3%)	16 (3.9%)	
T2	122 (13.8%)	69 (16.9%)	
T3	478 (54.1%)	197 (48.2%)	
T4	227 (25.7%)	127 (31.1%)	
T category			0.796
T1+2	178 (20.1%)	85 (20.8%)	
T3+4	705 (79.9%)	324 (79.2%)	
N category			0.065
N0	100 (11.3%)	29 (7.1%)	
N1	375 (42.5%)	167 (40.8%)	
N2	332 (37.6%)	174 (42.5%)	
N3	76 (8.6%)	39 (9.5%)	
Clinical Stage			0.055
II	76 (8.6%)	36 (8.8%)	
III	526 (59.6%)	216 (52.8%)	
IV	281 (31.8%)	157 (38.4%)	
Chemotherapy			
CCRT	454 (51.4%)	191 (46.7%)	0.115
IC+CCRT	429 (48.6%)	218 (53.3%)	
Anti-EGFR			<0.001
Without	595 (67.4%)	355 (86.8%)	
With	288 (32.6%)	54 (13.2%)	

IC, induction chemotherapy; CCRT, concurrent chemoradiotherapy.

recategorized T stage as a binary variable (T1–2 and T3–4) before entering the Cox regression, the correlation between T stage and the interval became statistically nonsignificant (Pearson chi-square test, P = 0.796). For the other remaining characteristics, there were no significant correlations between them and the radiation duration.

Prognosis

The 5-year overall survival rate was significantly lower for patients with radiation duration >7 weeks than for those completing radiation within 7 weeks (87.2% *vs.* 78.4%, P < 0.001; **Figure 1D**). The 5-year locoregional recurrence-free rate (93.2% *vs.* 87.0%, P < 0.001; **Figure 1A**), 5-year distant metastasis-free survival rate (89.4% *vs.* 84.4%, P = 0.026; **Figure 1B**) and progression-free survival rate (79.8% *vs.* 70.6%, P < 0.001; **Figure 1C**) were also significantly lower for patients with radiation duration ≤ 7 weeks than for those with duration > 7 weeks.

All 1292 patients were analyzed by univariate and multivariable Cox regression models. We included radiation duration (≤ 7 weeks vs. > 7 weeks), sex, age, T stage, N stage, anti-EGFR treatment (received vs. did not receive) and concurrent chemotherapy (with or without induction chemotherapy) in the model. Univariate Cox regression analysis showed that radiation duration (≤ 7 weeks vs. > 7 weeks), sex, age, T stage, N stage, and anti-EGFR treatment were found to have prognostic significance for OS. For DMFS, radiation duration (≤ 7 weeks vs. > 7 weeks), sex, N stage and received anti-EGFR treatment were found to have prognostic significance. Radiation duration (≤ 7 weeks vs. > 7 weeks), age, N stage and received anti-EGFR treatment were found to have prognostic significance for PFS. Only radiation duration (≤ 7 weeks vs. > 7 weeks) and N stage had prognostic significance for LRRFS (**Table 2**). Multivariate analysis indicated that radiation duration (≤ 7 weeks vs. > 7 weeks) was an independent prognostic factor for DMFS, LRRFS, PFS and OS (**Table 3**).

DISCUSSION

It was expected that a prolonged radiation duration was related to unfavorable clinical outcomes based on several studies that confirmed the benefit on tumor control and survival when radiotherapy for head and neck cancer was given without interruptions (4, 6, 7). Our study demonstrated that a longer duration of radiotherapy was an independent factor in NPC patients. Both univariate and multivariate analyses revealed that prolonged radiation duration > 7 weeks was a negative prognostic factor for DMFS, LRRFS, PFS and OS for NPC compared to the interval ≤ 7 weeks. It is important to raise awareness of prolonged radiation time for decision makers in clinical practice.

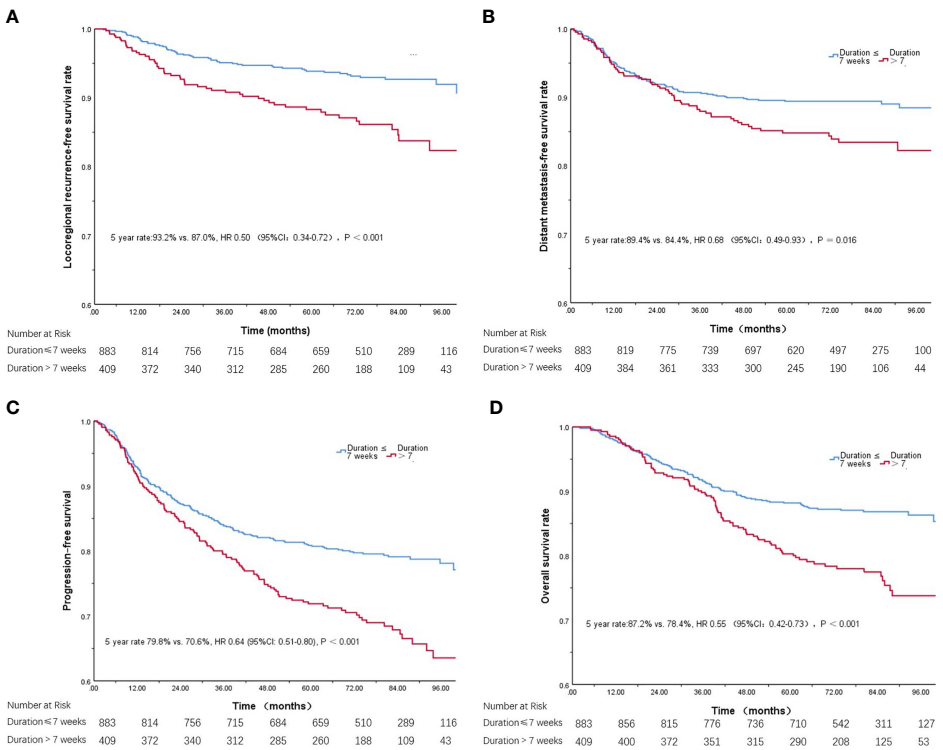

FIGURE 1 | Kaplan-Meier curves of locoregional recurrence-free survival **(A)**, distant metastasis-free survival **(B)**, progression-free survival **(C)**, and overall survival **(D)**, with radiation duration ≤ 7 weeks or >7 weeks.

TABLE 2 | Prognostic factors associated with overall survival by univariate Cox regression model (N=1292).

	DMFS				LRRFS				PFS				OS			
	B	**SE**	**HR (95%CI)**	***P***	**B**	**SE**	**HR (95%CI)**	***P***	**B**	**SE**	**HR (95%CI)**	***P***	**B**	**SE**	**HR (95%CI)**	***P***
Sex																
Female		1				1				1				1		
Male	-0.802	0.245	0.448 (0.278-0.725)	*0.001*	0.185	0.211	1.203 (0.795-1.819)	0.381	-0.325	0.147	0.722 (0.542-0.963)	0.027	-0.457	0.190	0.633 (0.436-0.919)	0.016
Radiation duration																
≤ 7 weeks		1				1				1				1		
> 7 weeks	-0.392	0.163	0.676 (0.491-0.931)	0.016	-0.704	0.188	0.495 (0.342-0.715)	<0.001	-0.452	0.115	0.636 (0.507-0.798)	<0.001	-0.591	0.142	0.554 (0.419-0.731)	<0.001
Age (continuous)	0.004	0.008	1.004 (0.989-1.020)	0.583	0.009	0.009	1.009 (0.990-1.027)	0.352	0.015	0.006	1.015 (1.004-1.026)	0.007	0.027	0.007	1.027 (1.013-1.041)	<0.001
Tumor stage																
T1		1				1				1				1		
T2	-0.295	0.380	0.745 (0.353-1.570)	0.439	-0.323	0.442	0.724 (0.305-1.721)	0.465	0.050	0.396	1.051 (0.484-2.285)	0.900	-0.812	0.349	0.444 (0.224-0.881)	0.020
T3	-0.381	0.264	0.684 (0.404-1.146)	0.148	0.133	0.265	1.142 (0.679-1.921)	0.616	-0.126	0.277	0.882 (0.513-1.517)	0.650	-0.769	0.226	0.463 (0.298-0.721)	0.001
T4	-0.299	0.181	0.742(0.520-1.056)	0.098	-0.456	0.221	0.634 (0.411-0.977)	0.039	-0.577	0.162	0.562 (0.409-0.772)	<0.001	-0.930	0.155	0.3695 (0.291-0.535)	<0.001
Node stage																
N0		1				1				1				1		
N1	-1.353	0.338	0.258 (0.133-0.501)	<0.001	-1.477	0.467	0.228 (0.090-0.580)	0.002	-1.238	0.262	0.290 (0.174-0.485)	<0.001	*-1.531*	0.331	0.216 (0.113-0.414)	<0.001
N2	-1.723	0.243	0.179 (0.111-0.288)	<0.001	-0.899	0.288	0.407 (0.231-0.716)	0.002	-1.038	0.176	0.339 (0.240-0.478)	<0.001	*-1.309*	0.206	0.270 (0.180-0.405)	<0.001
N3	-0.813	0.209	0.444 (0.295-0.668)	<0.001	-0.634	0.282	0.531 (0.305-0.923)	0.025	-0.604	0.167	0.547 (0.394-0.759)	<0.001	*-0.812*	0.194	0.444 (0.304-0.649)	<0.001
Anti-EGFR																
Without		1				1				1				1		
With	0.440	0.203	1.553 (1.043-2.313)	*0.030*	-0.135	0.207	0.874 (0.583-1.312)	0.516	0.353	0.140	1.424 (1.081-1.875)	0.012	0.664	0.193	1.943 (1.331-2.835)	0.001
Induction chemotherapy																
CCRT		1				1				1				1		
IC+CCRT	0.116	0.161	1.123 (0.819-1.538)	0.472	-0.368	0.190	0.692 (0.477-1.005)	0.053	-0.129	0.114	0.879 (0.703-1.098)	0.256	-0.226	0.141	0.798 (0.605-1.053)	0.110

OS, Overall survival; DMFS, Distant metastasis–free survival; LRRFS, locoregional relapse–free survival; PFS, progression–free survival; IC, induction chemotherapy; CCRT, Concurrent chemoradiotherapy.

TABLE 3 | Multivariate analyses of factors based on the Cox regression model.

Outcomes	Variables in the final model	B	SE	HR (95%CI)	P
DMFS					
	Tumor stage				
	T1				
	T2	-0.310	0.387	0.734 (0.343-1.568)	0.424
	T3	-0.695	0.272	0.499 (0.293-0.850)	0.011
	T4	-0.366	0.185	0.694 (0.483-0.997)	0.048
	Node stage				
	N0				
	N1	-1.502	0.344	0.223 (0.113-0.437)	<0.001
	N2	-1.854	0.248	0.157 (0.096-0.255)	<0.001
	N3	-0.908	0.212	0.403 (0.266-0.612)	<0.001
	Induction chemotherapy				
	CCRT				
	IC+CCRT	0.405	0.168	1.500 (1.078-2.086)	0.016
	Radiation duration				
	≤ 7 weeks				
	> 7 weeks	-0.362	0.165	0.696 (0.504-0.962)	0.028
LRRFS					
	Node stage				
	N0				
	N1	-1.346	0.481	0.260 (0.101-0.669)	0.005
	N2	-0.823	0.292	0.439 (0.248-0.779)	0.005
	N3	-0.603	0.284	0.547 (0.314-0.955)	0.034
	Radiation duration				
	≤ 7 weeks				
	> 7 weeks	-0.637	0.190	0.529 (0.365-0.768)	<0.001
PFS					
	Age (continuous)	0.011	0.005	1.011 (1.001-1.022)	0.037
	Tumor stage				
	T1				
	T2	-0.622	0.297	0.537 (0.300-0.962)	0.036
	T3	-0.463	0.180	0.629 (0.442-0.895)	0.010
	T4	-0.565	0.131	0.568 (0.440-0.734)	<0.001
	Node stage				
	N0				
	N1	-1.299	0.266	0.273 (0.162-0.459)	<0.001
	N2	-1.127	0.179	0.324 (0.228-0.460)	<0.001
	N3	-0.634	0.169	0.530 (0.381-0.739)	<0.001
	Radiation duration				
	≤ 7 weeks				
	> 7 weeks	-0.382	0.117	0.682 (0.543-0.857)	<0.001
OS					
	Age (continuous)	0.021	0.007	1.021 (1.008-1.035)	0.007
	Tumor stage				
	T1				
	T2	-0.765	0.355	0.465 (0.232-0.932)	0.031
	T3	-0.942	0.233	0.390 (0.247-0.615)	<0.001
	T4	-0.943	0.159	0.393 (0.288-0.536)	<0.001
	Node stage				
	N0				
	N1	-1.668	0.336	0.189 (0.098-0.364)	<0.001
	N2	-1.404	0.210	0.246 (0.163-0.371)	<0.001
	N3	-0.863	0.196	0.422 (0.287-0.620)	<0.001
	Radiation duration				
	≤ 7 weeks				
	> 7 weeks	-0.505	0.143	0.604 (0.456-0.799)	<0.001

OS, Overall survival; DMFS, Distant metastasis–free survival; LRRFS, locoregional relapse–free survival; PFS, progression–free survival.

The general consensus for radiotherapy is that treatment should be given without interruptions. In real clinical practice, there are always some reasons for prolonged radiation time. Several studies have also demonstrated the impact of a longer duration of radiation treatment on local failure risk and overall survival in patients with NPC and other types of cancers (12–15), and in these studies, radiation is conventional radiotherapy. This phenomenon has been proven in both xenograft animal models

and clinical studies with cervical cancer, bladder cancer and head and neck cancer (15–17). For NPC, a study published by Hong Kong researchers confirmed that interruptions in radiation and the prolongation of radiation adversely affect outcomes in radiotherapy (7). Other studies have also demonstrated the impact of prolonged radiation duration on local control risk and overall survival in patients with head and neck cancers (18, 19). We must note that previous studies were all based on conventional radiotherapy. Our present study is based on IMRT, and the results show that the estimated 5-year locoregional relapse-free survival, distant metastasis-free survival, progression-free survival and overall survival in patients with radiation ≤ 7 weeks *versus* patients with radiation > 7 weeks were 93.2% *versus* 87.0% ($P < 0.001$), 89.4% *versus* 84.4% ($P = 0.016$), 79.8% versus 70.6% ($P < 0.001$) and 87.2% *versus* 78.4% ($P < 0.001$), respectively. The results demonstrated that those patients who finished their radiotherapy on schedule had a better outcome than those who had interruptions during their radiotherapy due to any issues. The reason for the association between the prolonged duration and prognosis of NPC patients is complex. One possible explanation is as follows: when treatment is interrupted, the repopulation and recycling of tumor cells can occur (16), which is believed to be a significant risk for treatment failure; however, this explanation needs further study, especially since IMRT is currently popular in clinical practice and the basic radiation biology of IMRT is still not well clarified, which seems to make this issue slightly more complex.

A clear understanding of the factors associated with a prolonged waiting time can aid clinicians in providing better care (6). The causes of unplanned treatment interruptions are likely complex and multifactorial. In general, the acute toxicity caused by radiation and chemotherapy is responsible for unplanned treatment interruptions (20). Studies have demonstrated that concurrent chemotherapy increases acute toxicity over radiotherapy alone (4). The most common treatment-related side effects that lead to unplanned treatment interruptions are severe mucositis and skin reactions (4). Some comorbid conditions are associated with delayed wound healing, especially poor nutritional status, vascular disease, and diabetes mellitus (21). Cisplatin-based concurrent chemotherapy can cause nausea, vomiting and other complications, while nedaplatin can achieve similar treatment benefits without too many complications. Some research studies have already shown that concurrent chemotherapy is associated with the greatest duration of radiotherapy (4, 11). To minimize the negative effect, supportive medications to improve symptoms such as odynophagia and severe skin reactions should be provided as early as possible. Another reason may be caused by shortage of radiotherapy facilities, although they are available worldwide, but are often inadequate to the population demands placed on them due to an increasing number of patients since cancer incidence has increased in various parts of the world. However, we must note another special factor in China: national long-term holidays, such as May Day holidays, National Days and Spring Festival holiday. All these holidays will cause an interruption of radiation duration to more than 7 days. In the present study, 61.9% of NPC patients with prolonged duration of radiotherapy (radiation duration >7 weeks) were associated with these holidays since radiation ceased at that time.

The strength of this study was that it was based a large patient population and intensity-modulated radiotherapy. We must admit that our study was limited by its retrospective and single center nature without external validation of the results. First, the presented data were derived from a single institution located in an endemic area with expertise in NPC. Second, there was no randomization; therefore, some imbalance is inevitable. However, based on the results of the present study, launching a prospective randomized clinical trial to elucidate the relationship between radiation duration and prognosis in NPC patients may be ethically unacceptable.

CONCLUSIONS

In conclusion, this study demonstrated that the prolonged duration of intensity-modulated radiotherapy is associated with a high risk of locoregional and distant failure and therefore the survival prognosis is worse for NPC patients, especially for patients with advanced N stages. Our present study may help clinical decision makers better understand this patient population and even apply these results to those with other head-and-neck cancers and take preventive measures to make optimal decisions on how to reduce the length of treatment in the future. And this also remind health workers should take proper solutions to minimize the disruptions during current pandemic of COVID-19.

DATA AVAILABILITY STATEMENT

The datasets presented in this study (RDDA2021001976) can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://www.researchdata.org.cn.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Sun Yat-sen University Cancer Center Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-YC and Y-JH conceived the study. D-HL and XZ made substantial contributions to data acquisition, LX, D-HL and Y-FO-Y analyzed the data and performed interpretation of data. LX, D-HL and Y-JH were involved in drafting the manuscript. Y-JH edited the manuscript. All authors contributed to the article and approved the submitted version.

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