

Advanced head and neck cancer: from organ preservation strategies to extended resections and reconstruction

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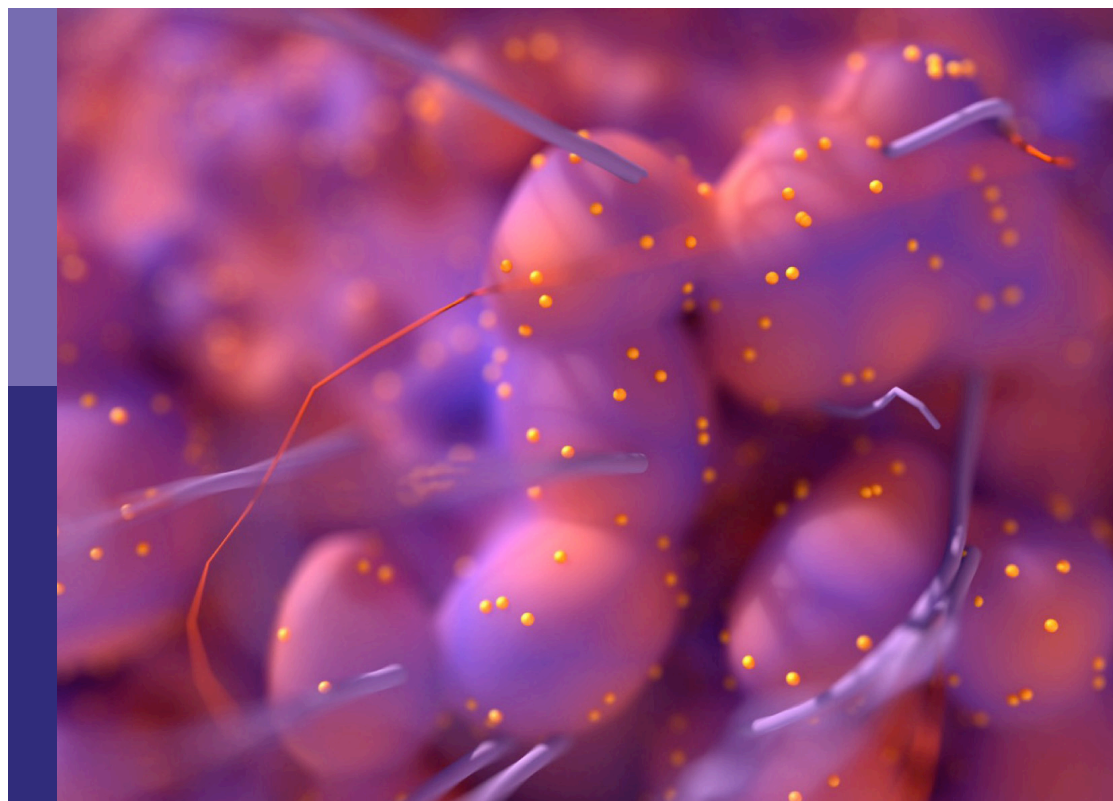
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Advanced head and neck cancer: from organ preservation strategies to extended resections and reconstruction

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The European Larynx Organ Preservation Study [MK-3475-C44]

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The European Larynx Organ Preservation Study (ELOS; NCT06137378) is a prospective, randomized, open-label, two-armed parallel group controlled, phase II multicenter larynx organ preservation (LOP) trial in locoregionally advanced (LA) stage III, IVA/B head and neck squamous cell carcinoma of the larynx or hypopharynx (LHSCC) amenable for total laryngectomy (TL) with PD-L1 expression within tumor tissue biopsy, calculated as CPS ≥ 1 . Induction chemotherapy (IC) with docetaxel and cisplatin (TP) followed by radiation will be compared to TP plus PD-1 inhibition by pembrolizumab (MK-3475; 200 mg i.v. starting day 1 q3w for 17 cycles). After a short induction early response evaluation (ERE) 21 $\pm$ 3 days after the first cycle of IC (IC-1), responders achieving endoscopic estimated tumor surface shrinkage (ETSS) $\geq 30\%$ will get an additional two cycles of IC followed by intensity-modulated radiotherapy 70–72 Gy (EQD2/ $\alpha/\beta = 10$) aiming at LOP. Nonresponders (ETSS < 30% or progressing disease) will receive TL and bilateral neck dissection followed by postoperative radiation or chemoradiation as recommended by the clinic's multidisciplinary tumor board. Pembrolizumab treatment will be continued in the intervention arm regardless of ETSS status after IC-1 in both responders and laryngectomized nonresponders, independent of subsequent decisions on adjuvant therapy after TL.

Clinical Trial Registration: clinicaltrials.gov, identifier NCT06137378.

KEYWORDS

head and neck squamous cell carcinoma (HNSCC), larynx and hypopharynx cancer (LHSCC), larynx organ preservation (LOP), total laryngectomy (TL), induction chemotherapy (IC), randomized controlled trial (RCT), larynx organ function, immune checkpoint blockade PD-1:PD-L1 axis

Introduction

The European Larynx Organ Preservation Study (ELOS) (1) is a prospective, randomized, open-label, two-armed parallel group controlled, phase II multicenter larynx organ preservation (LOP) trial in locoregionally advanced (LA) stage III, IVA/B squamous cell carcinoma of the larynx or hypopharynx (LHSCC) with PD-L1 expression within tumor tissue biopsy, calculated as CPS ≥ 1 , amenable for total laryngectomy (TL). Large stage II hypopharyngeal LHSCCs only resectable by total laryngopharyngectomy are also eligible. Induction chemotherapy (IC) with docetaxel and cisplatin (TP) followed by radiation will be compared to TP and additional PD-1 inhibition. Patients will be selected after a short induction early response evaluation (ERE) after the first cycle of IC (IC-1) aiming at LOP by additional two cycles of IC followed by radiotherapy (RT) for responders achieving endoscopic estimated tumor surface shrinkage (ETSS) $\geq 30\%$ (1–3). Nonresponders (ETSS $< 30\%$ or progressing disease) will receive TL and neck dissection (ND), preferably ipsilateral and contralateral selective neck dissection (SND), followed by postoperative radiation (PORT) or cisplatin-based concurrent chemoradiation (PORCT) according to the recommendation of the clinic's multidisciplinary tumor board (MDTB). However, patients randomized into the intervention arm will receive pembrolizumab (MK-3475) 200 mg i.v. starting at day 1 and in a 3-week cycle (q3w) for up to 17 cycles (12 months). Treatment with pembrolizumab will continue in the experimental arm regardless of ETSS status after IC-1 in both responders and laryngectomized nonresponders, independent of subsequent decisions on adjuvant therapy after TL.

The primary objective of ELOS is to compare laryngectomy-free survival (LFS) achieved by adding pembrolizumab (KEYTRUDA®) to standard treatment and LFS after standard treatment according to the DeLOS-II protocol in advanced LHNCC curable by TL. Hypothesis: Adding PD-1 inhibition by pembrolizumab to organ preservation chemoradiation treatment improves LFS compared to standard treatment according to the DeLOS-II protocol.

The secondary objectives are to compare quality of swallowing (QoS) assessed by fiber-endoscopic assessment of swallowing (FEES), event-free survival (EFS), and overall survival (OS) achieved by adding pembrolizumab to standard treatment and QoS, EFS, and OS after standard treatment according to the DeLOS-II protocol in advanced LHSCC.

In general, the main interest in trials focusing on improving quality and degree of LOP is late functional (in particular "swallowing") outcome. Current instruments assessing health-related QoL are less meaningful than direct objective assessment of swallowing utilizing physical examination like FEES. FEES is a well-approved and reliable method and allows clear scoring of QoS for instance by applying the Rosenbek Scale (4). Therefore, the investigators decided to avoid any questionnaires for this assessment including those approved for use in head and neck cancer, as they fail in specifically addressing the main study outcome, functional LOP.

Hypothesis: Adding PD-1 inhibition by pembrolizumab to organ preservation chemoradiation treatment improves QoS, EFS, and OS compared to standard treatment according to the DeLOS-II protocol. EFS events are defined as any event interfering with either

proper larynx organ function (independent of the cause, tumor or treatment related), relapse (local, loco-regional, or distant), or death. However, TL in nonresponders with ETSS $< 30\%$ is per-protocol defined treatment, and early salvage TL is not considered as an event in the EFS analyses with alternative EFS definition.

Preceding ELOS, the German multicenter randomized phase-II LOP trial DeLOS-II (2) was performed to investigate the impact of cetuximab added to induction chemotherapy and radiation on LFS in LA LHSCC. Untreated patients with stage III/IV LHSCC amenable to TL were randomized to three cycles of IC with TP (docetaxel and cisplatin 75 mg/m²/day for day 1) followed by RT without (A) or with (B) standard dose cetuximab for 16 weeks. (The initially used TPF regimen 5-FU 750 mg/m²/day for days 1–5 was replaced with TP; this reduced acute toxicity and had no impact on response rate and outcome (2).) Response to the first IC cycle with ETSS $\geq 30\%$ was used to define early responders; early salvage TL was recommended to nonresponders. The primary objective (24-month LFS above 35%) was equally met by arms A (40/85, 47.1%) and B (41/88, 46.6%). The 24-month OS rates were 68.2% and 69.3% (2).

The PD-1:PD-L1 pathway is an attractive target for therapeutic intervention for LOP in LA LHSCC that can only be cured by surgery with TL and ND followed by RT or radiochemotherapy. However, LA LHSCC requires an immediate reduction of bulk tumor masses that can be best achieved by an IC with cisplatin (P) combined with 5-fluorouracil (F) or a taxane (T), most preferably docetaxel. The triple combination TPF, however, puts LHSCC patients at increased risk for serious adverse events and fatal outcome in up to 8% of patients (2). Therefore, and as shown in DeLOS-II, the omission of F and the use of TP for IC reduces side effects and the number of fatal events, by maintaining the efficacy of IC (2). Moreover, partial response according to ETSS $\geq 30\%$ achieved through TP had the highest positive predictive value for oncologic safety and successful LOP in this patient population.

Methods

Study design

ELOS is a prospective, randomized, open-label, two-armed parallel group controlled, phase II multicenter LOP trial with randomization in a 1:1 ratio into standard arm versus investigational arm receiving pembrolizumab with a flexible follow-up of 24–48 months. The design of ELOS is shown in Figure 1.

Arm A is the standard-treatment arm with no intervention (control). Patients randomized into arm A will receive a short induction treatment with a single cycle TP (IC-1) (T = docetaxel 75 mg/m² i.v. day 1, P = cisplatin 75 mg/m² i.v. day 1). Response evaluation will be performed in week 4 (day 21 $\pm$ 3 days) after IC-1 by endoscopic estimation of tumor-surface shrinkage (ETSS) to select nonresponders for early TL. Consequently, nonresponders will undergo TL and receive adjuvant RT or chemo-radiotherapy (CRT) according to the decision of the clinic's MDTB. Responders with ETSS $\geq 30\%$ receive additional two cycles of TP (IC-2 in week 4 $\pm$ 3 days and IC-3 in week 7 $\pm$ 3 days; same doses as IC-1) followed

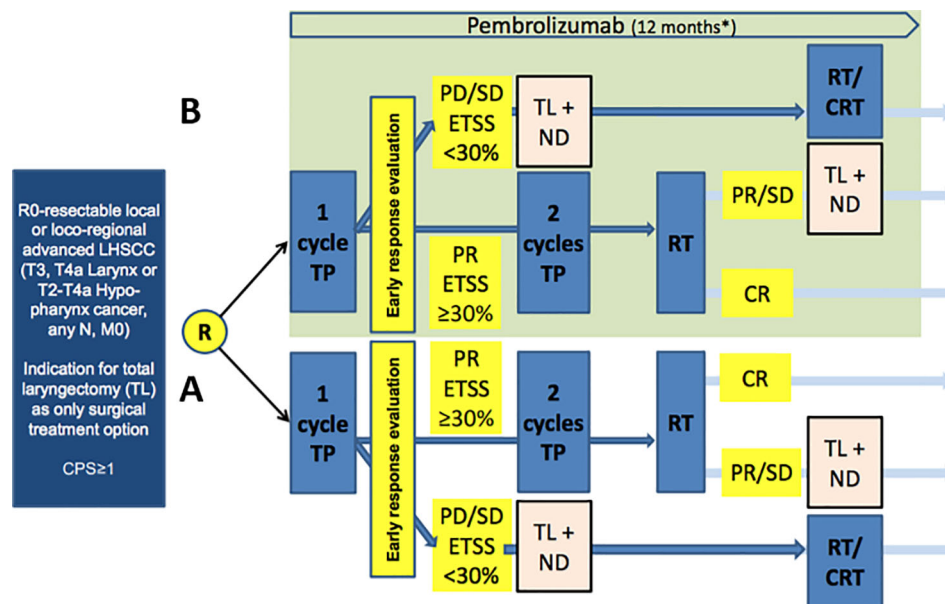


FIGURE 1

Study design of European Larynx Organ Preservation Study (ELOS) [MK-3475-C44] (NCT06137378), a randomized controlled trial comparing the outcome of patients in arm A (control) treatment according to the medication and radiation protocol as in the DeLOS-II LOP trial (2) with the same treatment plus additional pembrolizumab (over 12 months) in the experimental arm (B; light green). CPS: combined positive score; R, randomization; TP, induction chemotherapy utilizing T, docetaxel, P, cisplatin (75 mg/m² each per cycle); Early response evaluation (ERE) according to DeLOS-II criteria: PR, partial response $\geq 30\%$ endoscopic tumor surface shrinkage (ETSS) after one cycle; PD/SD, progressing disease or insufficient response $< 30\%$ ETSS; TL, total laryngectomy; ND, neck dissection; RT, radiotherapy; CRT, concomitant cisplatin-based chemo-radiotherapy.

by RT starting at week 11. Radiotherapy (RT) will be carried out using intensity-modulated radiotherapy (IMRT) with a total dose of 70–72 Gy (EQD2/ $\alpha/\beta = 10$) to all macroscopic tumor localizations. The elective neck nodal levels should be treated with 45–54 Gy depending on the risk of recurrence.

Arm B is the experimental arm receiving the only intervention, KEYTRUDA® (pembrolizumab). The treatment is the same as that for patients randomized into the standard arm A plus additional i.v. application of pembrolizumab in a 3-week cycle (q3w) of 200 mg each, starting on day 1 for up to 17 cycles (12 months). The treatment with pembrolizumab will continue in the experimental arm regardless of ETSS status after IC-1 in both responders and laryngectomized nonresponders, independent of subsequent decisions on adjuvant therapy with RT or CRT after TL.

Study population

Based on statistical considerations according to LFS in DeLOS-II, a sample of 140 patients with LA LHSCC resectable only by TL was planned to be recruited according to the following selection criteria.

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male and female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of squamous cell carcinoma (SCC) of the larynx or hypopharynx according to the decision of the MDTB suitable for TL can be enrolled in this study.
2. Stage II (large cT2 cN0 hypopharynx cancer only) and III, IVA, or IVB, whenever clear resection margins R0 > 5 mm can be achieved and no radiologic signs of extranodal extension of neck nodes are present.
3. Have provided newly obtained excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides.
4. PD-L1-expression* within the tumor biopsy, CPS ≥ 1 .
5. Male participants

A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

6. Female participants

A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

1. Not a woman of childbearing potential (WOCBP) OR.
2. A WOCBP who agrees to follow the contraceptive guidance during the treatment period and for at least 120 days after the last dose of study treatment.

7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation/randomization.
8. Have adequate organ function as defined in Table 4 of the protocol (Table 1). Specimens must be collected within 10 days prior to the start of study treatment.

* As predetermined by the EMA, the assessment of PD-L1 status has to be performed according to the guidelines for first-line treatment of head and neck cancer with pembrolizumab by using the CE-certified PD-L1 IHC 22C3 pharmDx assay (Agilent).

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP who has a positive urine pregnancy test within 72 h prior to receiving the first dose of study medication (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another

- stimulatory or co-inhibitory receptor on T or NK cells (e.g., CTLA-4, OX 40, and CD137).
3. Has received prior systemic anti-cancer therapy including investigational agents.
4. Has received prior RT.
5. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
6. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention.
7. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.
8. Has known distant metastases including active CNS metastases and/or carcinomatous meningitis.
9. Has severe hypersensitivity ($\geq$ grade 3) to pembrolizumab and/or any of its excipients.
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with the use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, among others) is not considered a form of systemic treatment and is allowed.
11. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has an active infection requiring systemic therapy.
13. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
14. Has a known history of hepatitis B [defined as hepatitis B surface antigen (HBsAg) reactive] or known active hepatitis C virus [defined as HCV RNA (qualitative) is detected] infection. Note: no testing for hepatitis B and hepatitis C is required unless mandated by the local health authority.
15. Has a known history of active TB (*Bacillus tuberculosis*).
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study or interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.
19. Has had an allogenic tissue/solid organ transplant.
20. Has a known intolerance to one of the substances administered during treatment including, e.g., antiemetics,

TABLE 1 Adequate organ function laboratory values for ELOS-eligible LHSCC patients.

System	Laboratory value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500/\mu\text{L}$
Platelets	$\geq 100,000/\mu\text{L}$
Hemoglobin	$\geq 9.0 \text{ g/dL}$ or $\geq 5.6 \text{ mmol/L}^a$
Renal	
Creatinine OR Measured or calculated ^b creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ OR $\geq 30 \text{ mL/min}$ for participant with creatinine levels $> 1.5 \times$ institutional ULN
Hepatic	
Serum total bilirubin	$\leq 1.5 \times \text{ULN}$ OR direct bilirubin $\leq \text{ULN}$ for participants with total bilirubin levels $> 1.5 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT), alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT), aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR, glomerular filtration rate; ULN, upper limit of normal. ^a Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

^b Creatinine clearance (CrCl) should be calculated per institutional standard.

or any other component of concurrent auxiliary medication (e.g., docetaxel or cisplatin).

Statistical methods

Estimation of sample size

Focusing on analyses of the impact of pembrolizumab, we propose a design as shown in the study schema with a 1:1 randomization ratio (at least 70 patients each arm). The patients in the control arm will be treated with the same doses of IC and IMRT as in DeLOS-II standard arm A (2) allowing for reliable comparison (outside protocol). In DeLOS-II, the LFS at 24 months was 47%. A delta of 19% in LFS at 24 months attributable to additional pembrolizumab resulting in 66% LFS would be of clinical significance. As ELOS is an early clinical trial, the one-sided significance level is chosen higher than the usual 2.5% level for confirmatory phase III trials. Based on calculations performed in nQuery 8, a sample size of 70 per group, with a total number of events of 72 required, with $\alpha = 0.05$ (one-sided significance level) in an exponential maximum likelihood test of equality of survival curves (according to the log-rank test) will have 81.1% power to detect a difference between the exponential parameters 0.378 (arm A, control group) and 0.208 (arm B, pembrolizumab). This corresponds to a constant hazard ratio (HR) = 1.817 and considers a common exponential dropout rate of 0.05 and flexible follow-up per patient, as described.

Randomization

Patients are randomized in a 1:1 ratio (70 treatment, 70 control) by minimization considering stratification by study center, localization of the primary lesion (larynx versus hypopharynx), and involvement of neck nodes (N0/N1 versus N2/N3 disease). A web-based solution for randomization (SecuTrial®) has been implemented.

Statistical principles

ELOS is an early clinical trial (phase II) to assess possible effect sizes. One-sided *p*-values lower than 5% will be considered significant. Both 90% and 95% confidence intervals (CIs) are reported for endpoints. All statistical analyses will test for superiority of the treatment arm adding pembrolizumab at a one-sided significance level of 5%. No statistical interim analyses are planned. The final analysis will be conducted after database lock that is scheduled to be exactly 24 months after randomization of the last patient.

The primary efficacy analysis as well as secondary efficacy analyses are based on the full analysis set (FAS), defined as all patients who were randomized. The FAS is analyzed following the intention-to-treat principle, in which every patient is analyzed as randomized.

Safety analyses are based on the safety analysis set (SAS) including all randomized patients who received at least one dose of study medication or standard of care.

Sensitivity analyses are performed on all patients completing the study adherent to the study protocol, referred to as the per-protocol (PP) population. The PP population consists of all patients without major protocol deviations.

Statistical analyses

Time-to-event endpoints (LFS, EFS, and OS) are analyzed using a Cox proportional hazards regression model with treatment and the stratification variables of the randomization [including study site, sex (male versus female), localization of the primary lesion (larynx versus hypopharynx), and involvement of neck nodes (N0/N1 versus N2/N3 disease)] as well as comorbidity according to the Charlson comorbidity index (5) as covariates. Analyses are conducted using the package survival from R with the corresponding function *coxph*. If the number of events is too small to fit the described model, a reduced model (i.e., including only the most important prognostic covariates assessed in univariate analyses) will be used. The treatment effect will be reported as HR with 90% and 95% CI and a *p*-value for the two-sided null hypothesis $H_0: HR = 1$. The primary endpoint and the secondary endpoints (Table 2) will be visualized as Kaplan–Meier curves. Sensitivity analyses will explore the robustness of these analyses. Missing data from time-to-event endpoints are dealt with using right censoring.

The Rosenbek scale is compared between treatment groups at 6 and 24 months using ordinal regression (package ordinal) with baseline, treatment, visit, and treatment-by-visit interaction. Proportions of patients at different score levels are reported with 95% CI. Shift differences from baseline and between treatments at 6 and 24 months are estimated using marginal means (package emmeans). Development of the Rosenbek scale over time is visualized using alluvial plots. A sensitivity analysis using mixed-models repeated measures (MMRM) is also conducted for the Rosenbek scale, with random patient intercept to account for dependent observations. Estimated marginal means are reported for group differences at 6 and 24 months. Missing data from the Rosenbek scale are dealt with using multiple imputation methods.

Safety analyses will follow standard procedures for the reporting of adverse events. We report safety analysis results as frequencies (percentages) by treatment group for the SAF. Descriptive reporting of laboratory parameters follows ICH E3 guidelines.

Discussion

ELOS investigates as a randomized controlled trial the potential benefit of PD-1 targeting by pembrolizumab added during the complete course of three cycles of TP-IC and RT and up to 12 months in total by comparing LFS and OS with the control arm utilizing three cycles of TP-IC (as in DeLOS-II). Each 3-week TP-IC cycle will start with docetaxel and cisplatin each with 75 mg/m² at day 1. Immediately after the third cycle of TP, RT will follow and a total dose of 70–72 Gy (EQD2/ $\alpha/\beta = 10$) will be administered by IMRT, as this protocol was shown to be safe and achieves good outcome (2). Nonresponders defined by ETSS < 30% after IC-1 will

TABLE 2 Objectives and related endpoints of the ELOS trial.

	Objective	Endpoint
Primary	Comparison of laryngectomy-free survival (LFS) between treatment groups	Hazard ratio in LFS between treatment groups
Secondary	Comparison of overall survival (OS) between treatment groups	Hazard ratio in OS between treatment groups
	Comparison of quality of swallowing (QoS) by fiber-optic endoscopic evaluation of swallowing (FEES)	Difference in proportions of patients in FEES categories assessed by Rosenbek scale at baseline and at months 6 and 24
	Comparison of event-free survival (EFS) between treatment groups	Hazard ratio in EFS between treatment groups
	Comparison of event-free survival (EFS) between treatment groups – alternative definition of EFS [†]	Hazard ratio in EFS between treatment groups
Safety	Compare safety of medication between treatment groups	Summary statistics of AE, SAE, and laboratory assessments

[†] As total laryngectomy (TL) in nonresponders with ETSS < 30% is per-protocol defined treatment, early salvage TL is not considered as an event in these analyses.

be recommended to receive early TL followed by adjuvant radio (chemo)therapy.

Additional pembrolizumab in chemoradiation protocols does not synergistically augment or stimulate hematologic or tissue affecting toxicity. The profile is more related to autoimmune effects like pneumonitis, colitis, and hypophysitis. Data from KEYNOTE-012 (7) suggest a moderate toxicity profile as described below.

The trade-off between expected increase of efficacy and moderate toxicity does not limit the meaning and rationale of the trial from a clinical and ethical view.

According to KEYNOTE-048, response to pembrolizumab monotherapy or added to platinum-based chemotherapy in first-line chemotherapy for recurrent and/or metastatic (R/M) HNSCC without curative treatment option was superior in patients with tumors expressing PD-L1 (CPS ≥ 1) and increased their survival (6). Consequently, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending on 17 October 2019 a change to the terms of the marketing authorization for pembrolizumab as monotherapy or in combination with platinum

and 5-fluorouracil (F) chemotherapy. Since then, pembrolizumab is indicated for the first-line treatment of R/M HNSCC in adults whose tumors express PD-L1 with a CPS ≥ 1 . Therefore, a prerequisite for using pembrolizumab in HNSCC in the EU is having a CPS ≥ 1 as stated in the inclusion criteria mentioned above.

Since PD-1 inhibition with pembrolizumab proved to be highly effective in second-line R/M HNSCC treatment (7–10) and first-line R/M HNSCC treatment (6), this new immune oncological checkpoint inhibitor therapy should be investigated in the curative setting including LOP trials. So far, pembrolizumab is in trials for its possible integration into primary standard therapy concepts for curative treatment of local advanced HNSCC (11, 12). At this time, final data for KEYNOTE-412 (11) and for ADRISK (12) and any data in this new indication (LOP) are not available yet. However, the results reported for KEYNOTE-412 (NCT03040999) at clinicaltrials.gov, despite failing to demonstrate superior event-free survival through added pembrolizumab, showed encouraging data (11). KEYNOTE-412 missed the pre-specified boundary of 0.0242 required for statistical significance according to the *p*-value of 0.0429 in the per-protocol defined stratified analysis. However, the HR of 0.83 with a two-sided 95% CI of 0.68 to 1.03 in a more heterogeneous population of LA HNSCC in a different setting (administered during definitive cisplatin-based radiochemotherapy) does not provide sufficient arguments against the use of pembrolizumab in an LOP trial. The LOP trial ELOS will be conducted according to the DeLOS-II protocol and hence is a very different therapy regimen as it utilizes a prolonged induction phase (up to three cycles of pembrolizumab simultaneous to TP-IC before the first irradiation). Indeed, ELOS will recommend early TL to all patients without sufficient ETSS < 30%, whereas only responders will receive three cycles of IC with cisplatin and additional docetaxel. Moreover, compared to KEYNOTE-412, ELOS will accrue a rather homogeneous cohort of HNSCC patients with narrower HNSCC characteristics. Indeed, neoadjuvant and adjuvant pembrolizumab achieved stronger responses in a higher frequency as observed in the first-line setting (14), and the combination of PD-1 immune-checkpoint blockade (ICB) with either neoadjuvant chemotherapy (15) or CTLA-4 ICB with ipilimumab in the IMCISION trial (16) demonstrated a high response rate including pathological responses without impairing resectability (16). Added docetaxel should further increase immunogenicity and anti-tumoral immune responses unleashed by pembrolizumab, and pembrolizumab indeed demonstrated high efficacy and safety in combination with paclitaxel and cisplatin in a single-arm phase II trial (17). Retrospective analyses of rather small cohorts treated with PD-1 ICB confirm these results in LA LHS CC (18) and LA hypopharyngeal cancer (13). Because of the encouraging data on survival mentioned above and the favorable PD-L1 expression as an inclusion criterion, pembrolizumab will also be continued in the experimental arm regardless of the response to IC with ETSS depending mostly on TP. All these reports on pembrolizumab in the neoadjuvant and adjuvant setting concluded that randomized controlled trials are urgently required to validate these rather general findings. Moreover, as all these reports so far

available did not include the standardized evaluation of larynx function and QoS in particular, we will conduct the randomized controlled ELOS trial to show increased LFS and QoS in LA LHSCC.

Benefit–risk assessment

Expected benefit

In approximately one-third of patients, standard TP IC followed by RT is unsuccessful, and their larynx must be removed via TL. Based on the current literature (2, 3, 5–10, 12–18), the investigators expect that pembrolizumab administration will facilitate LOP and OS by allowing more patients to preserve their larynx and a permanent prevention of cancer recurrence even in laryngectomized nonresponders by administering pembrolizumab over a period of 1 year. In addition to the benefit for the patients included, the results of the study may help to contribute to the future treatment of patients with LA LHSCC.

Risks and burdens

The investigational medicinal product pembrolizumab may have side effects that may or may not increase the risk for adverse events of standard IC + RT therapy. However, there are no reports about an increased risk for adverse events exceeding those expected from TP alone (13–15, 17, 18). Since pembrolizumab has a marketing authorization in Germany as well as worldwide for the treatment of various tumor diseases including HNSCC, many side effects are already known (6–9, 11, 13, 17, 18). The most common side effects of pembrolizumab are diarrhea, nausea, itching, rash, fatigue, and inflammation in the body caused by the highly activated immune system (autoimmune reactions), all mostly at grade 1 or 2 according to CTCAE (19). In addition, the as-yet untested combination of pembrolizumab with docetaxel and cisplatin may cause additional adverse effects that have not been previously reported. However, we expect these to be in the range reported for pembrolizumab combined with paclitaxel and cisplatin (16–18) and not exceeding those observed in the DeLOS-II trial (2). However, treatment is discontinued if there is progression of the disease, if the patient cannot tolerate the treatment, or if the patient so desires.

All examinations performed as part of the study are examinations that are usually performed as part of the standard treatment of the disease and do not pose any identifiable additional risk. The potential benefit of participating in ELOS should be considered higher than the potential risk.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the University of Rostock (P_00432; date of approval: 2023-11-09). The ELOS study protocol was registered as CTIS 2022-502751-6100 in the clinical trial information system (CTIS) of the European Medical Agency (EMA) and approved by the German Paul Ehrlich Institute (PEI) on behalf of the reporting

Member State (rMS) and included independent review and approval by the Ethics Committee of the University of Rostock (P_00432). The study is conducted in accordance with the local legislation and institutional requirements. The participants provide their written informed consent to participate in this study.

Author contributions

GW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TW: Conceptualization, Investigation, Methodology, Project administration, Validation, Writing – review & editing. MP: Investigation, Project administration, Writing – review & editing. JN: Methodology, Project administration, Supervision, Writing – review & editing. IM: Methodology, Software, Writing – review & editing. TA: Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. RT: Project administration, Writing – review & editing. JV: Investigation, Methodology, Project administration, Writing – review & editing. KV: Investigation, Writing – review & editing. SM: Methodology, Writing – review & editing. MS: Investigation, Writing – review & editing. VZ: Investigation, Writing – review & editing. NN: Investigation, Methodology, Supervision, Writing – review & editing. TK: Investigation, Methodology, Supervision, Writing – review & editing. PH: Investigation, Writing – review & editing. OG-L: Investigation, Supervision, Writing – review & editing. JK: Investigation, Supervision, Writing – review & editing. SW: Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. AD: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

Some of the authors disclosed potential conflicts of interest. GW discloses honoraria for lectures from Merck KGaA, outside the submitted work; OG-L declares financial Interests, Personal, Invited Speaker: Novartis, Merz, and MedEL; Financial Interests, Personal, Advisory Board: Merz; Financial Interests, Personal and Institutional, Research Grant: MedEL; Financial Interests, Personal and Institutional, Funding: MedEL. JK reports personal fees from Merck KGaA, outside the submitted work. SW declares remuneration for scientific presentations or participation on Advisory Boards for MSD, BMS, Merck Serono, Roche, AstraZeneca, Sanofi, and GSK. AD reports remuneration for

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The remaining 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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Assessing the role of advanced artificial intelligence as a tool in multidisciplinary tumor board decision-making for recurrent/metastatic head and neck cancer cases – the first study on ChatGPT 4o and a comparison to ChatGPT 4.0

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Background: Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) is characterized by a complex therapeutic management that needs to be discussed in multidisciplinary tumor boards (MDT). While artificial intelligence (AI) improved significantly to assist healthcare professionals in making informed treatment decisions for primary cases, an application in the even more complex recurrent/metastatic setting has not been evaluated yet. This study also represents the first evaluation of the recently published LLM ChatGPT 4o, compared to ChatGPT 4.0 for providing therapy recommendations.

Methods: The therapy recommendations for 100 HNSCC cases generated by each LLM, 50 cases of recurrence and 50 cases of distant metastasis were evaluated by two independent reviewers. The primary outcome measured was the quality of the therapy recommendations measured by the following parameters: clinical recommendation, explanation, and summarization.

Results: In this study, ChatGPT 4o and 4.0 provided mostly general answers for surgery, palliative care, or systemic therapy. ChatGPT 4o proved to be 48.5% faster than ChatGPT 4.0. For clinical recommendation, explanation, and summarization both LLMs obtained high scores in terms of performance of therapy recommendations, with no significant differences between both LLMs, but demonstrated to be mostly an assisting tool, requiring validation by an experienced clinician due to a lack of transparency and sometimes recommending treatment modalities that are not part of the current treatment guidelines.

Conclusion: This research demonstrates that ChatGPT 4o and 4.0 share a similar performance, while ChatGPT 4o is significantly faster. Since the current versions cannot tailor therapy recommendations, and sometimes recommend incorrect treatment options and lack information on the source material, advanced AI models at the moment can merely assist in the MDT setting for recurrent/metastatic HNSCC.

KEYWORDS

HNSCC, multidisciplinary tumorboard, salvage surgery, artificial intelligence, ChatGPT

1 Introduction

Despite recent advancements in immuno-oncology, the five-year survival rate for Head and Neck Squamous Cell Carcinoma (HNSCC) remains poor with approximately 50-60% (1, 2). Recurrence is common in patients with an HNSCC, and the therapy options are limited, resulting in a median overall survival of only 11.8 months (2, 3). Salvage surgery, re-irradiation, and systemic therapies, including cisplatin-based regimens and immunotherapeutic agents, constitute the primary therapeutic options. Additionally, some of the patients already present with distant metastasis at the time of diagnosis limiting the therapy options even further (4). Given that some patients respond well to treatment, while a significant proportion of patients experiences recurrence, each patient is discussed in a multidisciplinary tumor board (MDT) (5, 6). MDTs are essential for providing a multidisciplinary and comprehensive perspective on each case, and for tailoring treatment plans to individual needs (7, 8). On the other hand, MDTs are limited by costs, responsibilities, geographic barriers, and treatment delays (7–9). These limitations have prompted research into artificial intelligence (AI).

AI, in the form of deep learning (DL) and natural language processing (NLP), has opened ways to use Large Language Models (LLMs) like Generative Pre-trained Transformer (GPT) (10, 11) for the MDT setting. While LLMs are constantly evolving, they are able to access large datasets in a short amount of time. Extracting information of recent studies, and the summarization of text are some of the main strengths of LLMs and could potentially be the basis of a modern approach to discuss oncological cases (7–9). This ability to organize and structure data could enable these tools to become an assistance, or even guide MDT-based decision making (10, 12). In the therapeutic and diagnostic setting of HNSCC, ChatGPT achieved an impressive performance in prior studies (12, 13). While most studies of LLMs identified limitations that need to be overcome, including a lack of transparency, the inability to customize therapy recommendations, and sometimes recommending therapy options that do not fully align with established clinical guidelines (12), LLMs are promising tools for enhancing clinical-decision making in the MDT setting of HNSCC.

This involves rapidly accessing and summarizing large volumes of clinical information and the latest research, offering evidence-based insights, and streamlining administrative tasks in a time-efficient manner (14). While the evaluation of LLMs lays the foundation of a clinical use in the future, the assessment of the performance is challenging (10). Using validated evaluation tools such as the Artificial Intelligence Performance Instrument (AIPI), is necessary to ensure the reliability, accuracy, and clinical relevance of its recommendations (15).

While prior studies investigated ChatGPT 3.5 and ChatGPT 4.0 for primary HNSCC cases (12, 13, 16, 17), ChatGPT-4 has not yet been evaluated in the decision-making process for recurrent/metastatic Head and Neck Squamous Cell Carcinoma (HNSCC). The novel ChatGPT 4o was just introduced a few weeks ago and is an AI model that is designed to offer enhanced capabilities over its predecessor, ChatGPT 4.0, potentially providing more accurate and contextually appropriate responses. The improvements in ChatGPT 4o include better understanding of more complex queries and improved contextual awareness (18, 19). These advancements suggest that ChatGPT 4o could offer significant benefits over ChatGPT 4.0 and the ability to potentially generate more tailored recommendations. The treatment of such complex cases demands a multidisciplinary approach, thorough knowledge of the latest literature and adherence to evolving clinical guidelines (20), providing a rigorous test of the LLMs capabilities. A comprehensive comparison between the performance of ChatGPT 4.0 and the more recent ChatGPT 4o will be conducted to evaluate the capabilities of ChatGPT 4o in offering therapy recommendations for patients with recurrent/metastatic HNSCC.

2 Materials and methods

2.1 Patient cohort

This study included patients with a verified recurrent/metastatic HNSCC diagnosis. The electronic patient file and MDT documents provided clinical and histological tumor characteristics before

treatment initiation. This study comprised a total of 100 consecutive patients, who have been treated at the Department of Otorhinolaryngology/Head and Neck Surgery, Klinikum rechts der Isar, Technical University of Munich. Recurrent cases were defined as patients who had a local or regional recurrence of HNSCC after initial treatment, with no evidence of distant metastasis at the time of recurrence. Metastatic cases were defined as patients who had distant metastasis beyond the head and neck region. This distinction was made based on imaging studies, histopathological biopsy results, and clinical records. Cases with local recurrence and distal metastasis at the same time were part of the distal metastasis group to differentiate between the two groups and the resulting different therapy options. Out of the patients with recurrence, 76% (38) of the patients had local and regional recurrence, while 12% (6) of the patients had local recurrence and 12% (6) of the patients had regional recurrence in this study. Exclusion criteria included patients with insufficient clinical data or patients who received experimental treatments. To ensure patient confidentiality, the data were anonymized before being shared with the researchers, rendering patient identification impossible. This study was approved by the ethics committee of the Technical University of Munich (Reference: 2024-184_1-S-NP). The characteristics of the patient cohort are depicted in Table 1.

TABLE 1 Overview of the patient cohort.

Total patients	100
Sex	
Male	78 (78%)
Female	22 (22%)
Recurrence	
Primary and lymphatic	38(76%)
Primary	6(12%)
Lymphatic	6(12%)
Distant Metastasis	
	50
Subsites	
Larynx	32 (32%)
Oropharynx	28 (28%)
Oral Cavity	16(16%)
Hypopharynx	10(10%)
Nasal cavity	8(8%)
Nasopharynx	4(4%)
Salivary glands	2(2%)
Prior therapy	
Surgery	84(84%)
R(C)Tx	16 (16%)

100 cases of HNSCC were evaluated in this study, with 50 cases of recurrence and 50 cases of distant metastasis. RCTx, radiochemotherapy.

2.2 Artificial intelligence/ChatGPT - prompt formatting and data evaluation

ChatGPT 4o and ChatGPT 4.0 are AI chatbots that are accessible to the public. These chatbots use transformer-based language models to generate human-like text responses. The interaction is based on users submitting questions (prompts) through a website interface. The LLMs analyze the contextual relationships between the words in the user’s query to formulate a response. In this study, various prompts were tested, and a standardized prompt format was employed to input patient information into the LLMs, simulating the presentation of an individual patient case in multidisciplinary team (MDT) meetings. Initially, eight prompt variations based on common clinical scenarios in recurrent and metastatic HNSCC were generated and tested with a small subset of 10 randomly selected cases to evaluate responses from both ChatGPT 4o and 4.0. The prompt design mirrored the case presentation format used in MDTs and was iterated several times. The iterations varied in terms of the amount of information and were continuously refined. Two independent reviewers assessed the responses of each prompt for clinical recommendation, explanation, and summarization, rating each on a scale from 1 to 5. The eight prompts and the average total score for the ten cases in the preliminary assessment stage is depicted in the Supplementary Table 2. The scales were originally introduced as a tool to evaluate the performance of ChatGPT in the MDT setting of breast cancer (21), but were used in a variety of other studies (22, 23), including the MDT setting of primary HNSCC (12). The tool consists of the three grading scales of summarization, clinical recommendation, and explanation, each ranging from grade 1 (Poor/Total Disagreement) until 5 (Excellent/Total Agreement). The grading scales are further explained and depicted in the Supplementary Material. This pilot scoring phase with multiple iterations led to scorer calibration and training of the two reviewers. The final prompt version reached the highest total score and was selected for providing consistent and accurate therapy recommendations for the main study.

The standard version of the final prompt was “The patient has a history of (XX) for a (XX) carcinoma and now presents with (XX) carcinoma. What treatment options are available and which option do you think leads to the best prognosis?”.

An exemplary prompt was: “The patient has a history of surgery for a cT1a cN0 cM0 glottic laryngeal carcinoma and now presents with a rcT3 rcN1 cM1 glottic laryngeal carcinoma. What treatment options are available and which option do you think leads to the best prognosis?”. No further interaction was initiated after this response; The LLMs prompt history was erased, and the next question was asked. The study design and is shown in a flowchart in Figure 1. The responses were collected, and subsequently evaluated using a double-blind method. The two independent reviewers were uninformed about which AI model stated the response. All reviewers independently scored the answers to mitigate subjective biases. The answers provided were assessed using the grading scales for Summarization, Clinical Recommendation, and Explanation, as employed by Sorin et al.,

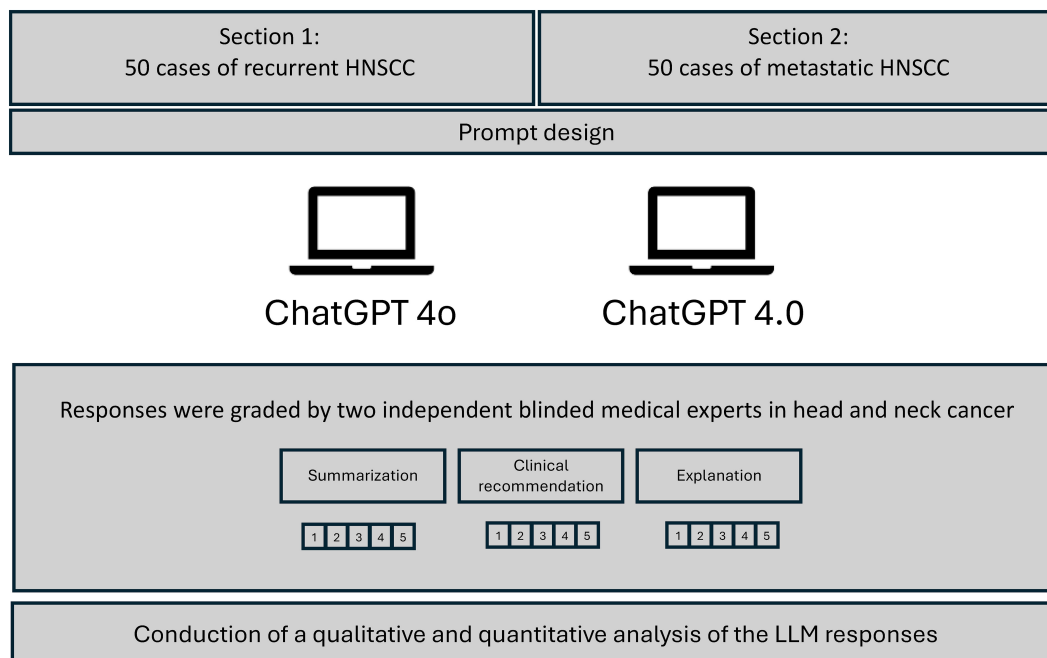


FIGURE 1

Flowchart of overall study design. Depiction of the grading of responses by ChatGPT 4o and ChatGPT 4.0. Evaluation of the responses by two independent reviewers.

2023 (21). Cohen's kappa coefficient was used to calculate the inter-rater reliability, providing a measure of the degree to which two raters agree in their categorization of items, corrected for chance agreement. For example, a Kappa value of 0.2 – 0.40 indicates fair agreement, a Kappa value of 0.41 – 0.60 indicates moderate agreement, a Kappa value of 0.61 – 0.80 indicates substantial agreement and a Kappa value of 0.81 – 1.00 indicates perfect agreement between the raters beyond what would be expected by chance. Mann–Whitney U test was used to identify significant differences between the performance of the responses of the two LLMs. A p-value of less than 0.05 was considered statistically significant. P-values were adjusted using the Bonferroni correction method when multiple hypothesis tests were conducted.

3 Results

ChatGPT 4o and ChatGPT 4.0 answered all prompts in this study in an exceptionally rapid manner. The mean inference speed for ChatGPT 4.0 was 29.7 seconds (± 2.84), while ChatGPT 4o exhibited a mean inference speed of 20.0 seconds (± 5.33), indicating an improved efficiency of 48.5%. For demonstration purposes exemplary responses generated by both LLMs are depicted in Figure 2. The design and presentation of the responses varied.

The responses from ChatGPT 4.0 and 4o involved the treatment modalities available for use in the recurrent setting, including salvage surgery and re-irradiation, while in the distant metastatic setting systemic therapy with chemotherapy including cisplatin,

carboplatin, and taxanes, targeted therapy, and immunotherapy with pembrolizumab or nivolumab were the most commonly stated answers. Additionally, also in the M1 situation measures of local control were highlighted such as palliative radiation, re-irradiation, salvage surgery, even though this was just recommended for alleviating symptoms such as airway obstruction. Both LLMs had the same primary therapy recommendation in 96% of the M1 cases (48 out of 50). In cases of recurrence, the therapy recommendation was matching in 86% (36 out of 50) of cases. The second choice of therapy was more heterogeneous, with only 38% (19 out of 50) cases matching in the M1 and recurrence situation.

The prognosis of the patients was deemed poor by ChatGPT sometimes even mentioning average five-year survival rates. The clinical history of each case was carefully described by both LLMs using the TNM classification and potential impact of each therapy option. When asked which therapy option leads to the best prognosis, salvage surgery was the most commonly recommended answer of both LLMs in the recurrent setting, but it was stated that this option is only viable for “rare cases where the disease is deemed resectable”. Salvage Neck Dissection was recommended by both LLMs when only lymph node recurrence was present, and in some cases of advanced rcT4b, a surgical approach was not recommended as the preferred treatment option including an explanation of potentially too radical/unfeasible surgery. Metastasis-Directed Surgery such as video-endoscopy assisted thoracoscopy for lung metastasis was mentioned in a few cases.

In both scenarios (recurrence and M1) the importance of multidisciplinary care involving medical oncologists, surgical oncologists, radiation oncologists, and palliative care specialists was highlighted. Especially integrated palliative care was a

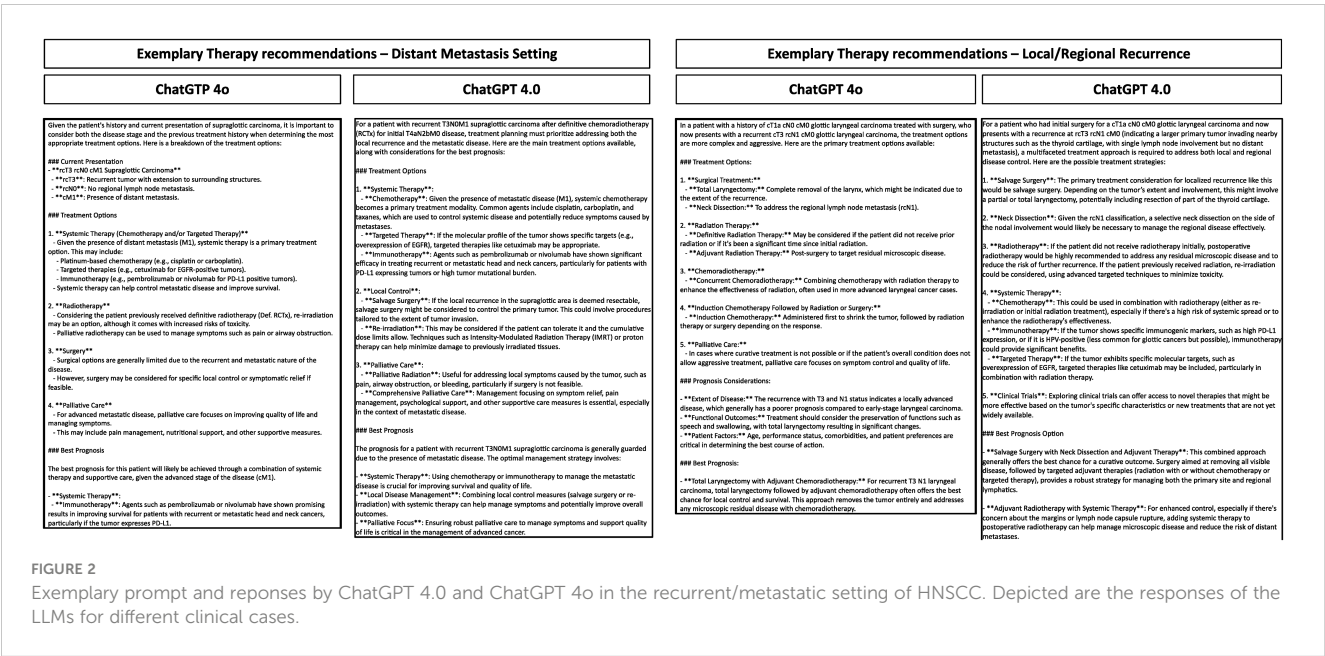


FIGURE 2 Exemplary prompt and reponses by ChatGPT 4.0 and ChatGPT 4o in the recurrent/metastatic setting of HNSCC. Depicted are the responses of the LLMs for different clinical cases.

cornerstone of therapy in almost all cases, with early integration for managing symptoms and improving quality of life rather than curative treatments. Both reviewers mentioned that the LLMs were able to call attention of the presence or lack of specific biomarkers, e.g., PD-L1, EBV DNA levels, to guide the choice of therapy. Important clinical studies for the use of immunotherapy were emphasized.

In only very few cases the therapy recommendation of the LLMs were not according to current guidelines. One of these cases is patient #1, who would have received surgery according to ChatGPT 4o even though the patient already had distant metastasis. Another example is patient #57, who would have received radiochemotherapy for lymph node recurrence by ChatGPT 4o. In case #55 of an rcT1 oral cavity cancer, one of the therapy options of both LLMs was observation and follow-up for a very small, well-differentiated tumor with clear margins post-resection, especially if further radiotherapy is deemed too risky.

When analyzing the recommended treatment options in detail, one recognizes differences between both LLMs even though the same prompt was used, and the prompt closely resembled the standardized way of presenting a patient at our MDT. An overview of the resulting therapy recommendations is depicted in Figure 3. ChatGPT 4o and 4.0 recommended surgery for 90% and 94% of recurrent cases as the first line of therapy, while systemic therapy was only recommended for a few select cases, such as a rcT4b case of oropharyngeal squamous cell carcinoma. Correspondingly, the second choice of therapy was systemic therapy for almost all patients (92% by ChatGPT 4o and 94% by ChatGPT 4.0), with the explicit recommendation of palliative care for one recurrent (rcT4b) case by ChatGPT 4.0. ChatGPT 4o on the other hand recommended the inclusion in a clinical trial for one patient as the second line therapy. In the distant metastatic setting, ChatGPT 4o and 4.0 recommended systemic therapy for 98% and 100% of patients. The second choice of therapy differed between both LLMs, with a recommendation of systemic therapy for 21% of

patients by ChatGPT 4o compared to 2% of patients using ChatGPT 4.0, and a recommendation of palliative care for 28% of patients by ChatGPT 4o and 90% of patients by ChatGPT 4.0. Palliative Care was never recommended as a first-choice therapy. Analyzing both the M1 and recurrent setting together, both LLMs recommended similar therapy options, with surgery for 23% vs 23.5% and systemic therapy for 27% vs 26.5% by ChatGPT 4o vs ChatGPT 4.0.

The performance of the LLMs for generating therapy recommendations for recurrent/metastatic HNSCC was evaluated by two independent reviewers. Overall, there was no significant difference in the performance of ChatGPT 4.0 and 4o, with both LLMs reaching similar scores for clinical recommendation (4.65 compared to 4.73, p=0.131), explanation (4.33 compared to 4.14, p=0.423), and summarization (4.12 compared to 4.28, p=0.204). Therefore, ChatGPT 4.0 achieved slightly better results in the explanation grade, while ranking lower in the clinical recommendation and summarization grades (Figure 4). In the analysis of recurrent HNSCC, there was also no significant difference in the performance in the grades of clinical recommendation (4.57 compared to 4.66, p=0.362), explanation (4.33 compared to 4.22, p=0.880), and summarization (4.14 compared to 4.27, p=0.200). The same was observed for the distant metastatic cases for clinical recommendation (4.72 compared to 4.79, p=0.214), explanation (4.33 compared to 4.05, p=0.317), and summarization (4.1 compared to 4.28, p=0.657). Clinical recommendation was graded better for cases with distant metastasis compared to the cases with local/regional recurrence. An overview of the statistical analysis is given in the Supplementary Table 1. When comparing the recommendations of ChatGPT 4o, two independent reviewers reached an agreement measured by Cohen's κ of 0.347 for summarization of text, of 0.255 for clinical recommendation, and 0.238 for explanation. When comparing the ChatGPT 4.0 recommendations, two independent reviewers reached an agreement measured by Cohen's κ of 0.383 for

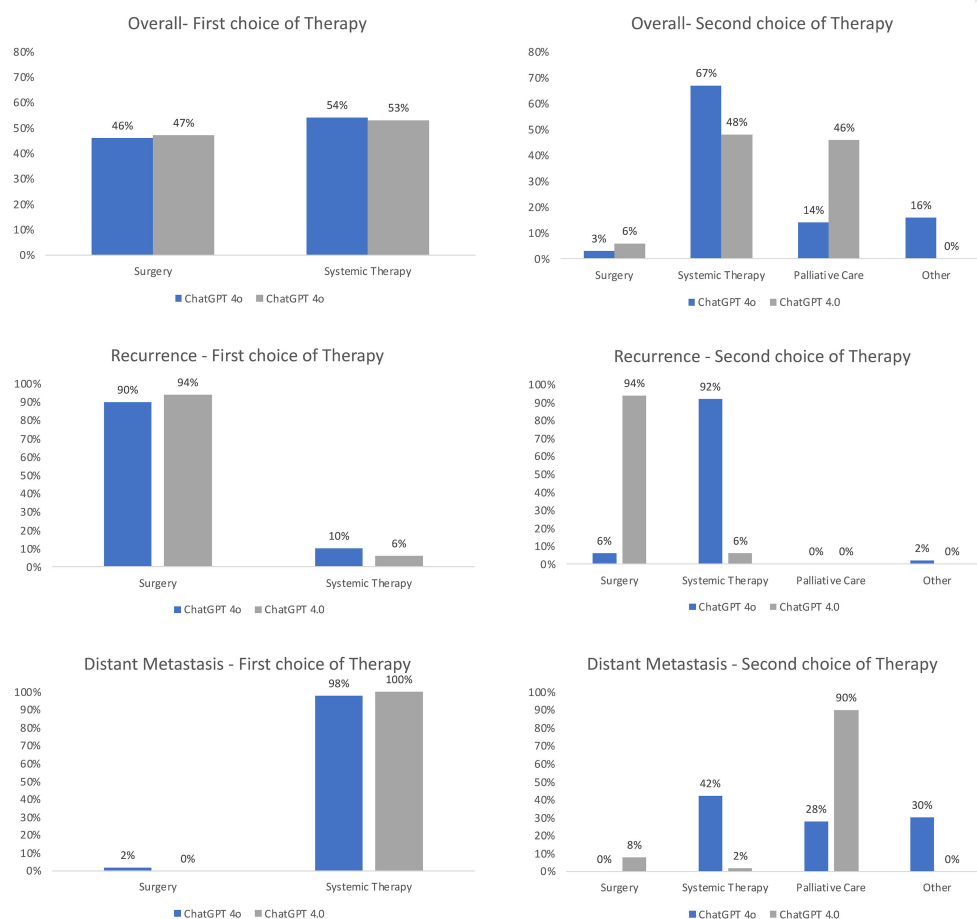


FIGURE 3

Overview of the recommended treatment options of ChatGPT 4o compared to ChatGPT 4.0. The answers of both LLMs were evaluated by two independent reviewers for the first choice and second choice therapy recommendations in the recurrent and distant metastatic setting. The results were normalized to 100%.

summarization of text, of 0.495 for clinical recommendation, and 0.518 for explanation on the decision made.

The different anatomical subsites out of the 50 cases were also analyzed in detail to explore potential areas of significant expertise (Figures 5, 6). The recommended therapy options differed only slightly between the anatomical subsites. The biggest difference was seen for the local/regional of OPSCC, in which ChatGPT 4o recommended surgery for 86% of the cases, compared to 93% when asked ChatGPT 4.0. For the recurrence of laryngeal cancer ChatGPT 4o recommended surgery for 94% of the cases, compared to 88% when asked ChatGPT 4.0. The results for cancer of the nasal cavity, nasopharynx and salivary glands are depicted in the Supplementary Material. There were also similar results in terms of the qualitative assessment of the overall performance among all subsites without a clear pattern of areas of special expertise, except for a maximum score of ChatGPT 4o for metastatic nasopharyngeal squamous cell carcinoma. This result is limited by the fact that only 4 cases of nasopharyngeal squamous cell carcinoma were included in this study.

Both LLMs refrained from giving precise recommendations, and highlighted, that they are not meant to give medical advice or

replace the opinion of a medical doctor. Additionally, both LLMs stated that “Each case should be individually assessed by a multidisciplinary team to tailor the treatment plan according to the patient’s specific disease characteristics, overall health status, and personal preferences, aiming to maximize quality of life and disease control”.

4 Discussion

This study represents the first evaluation and comparison of ChatGPT 4o and 4.0 in the currently largest dataset of recurrent/metastatic (R/M) HNSCC. Both LLMs engaged in discussions about the therapy options of these patients, stating potential challenges and the main characteristics of each treatment. The performance for giving therapy recommendations of the LLMs was compared and evaluated by two independent reviewers. The objective of this study was to investigate the potential and limitations of the current landscape of advanced LLMs and to assess a potential use in the multidisciplinary tumor board (MDT) setting. LLMs as a subset of artificial intelligence (AI) focus on the analysis of human language

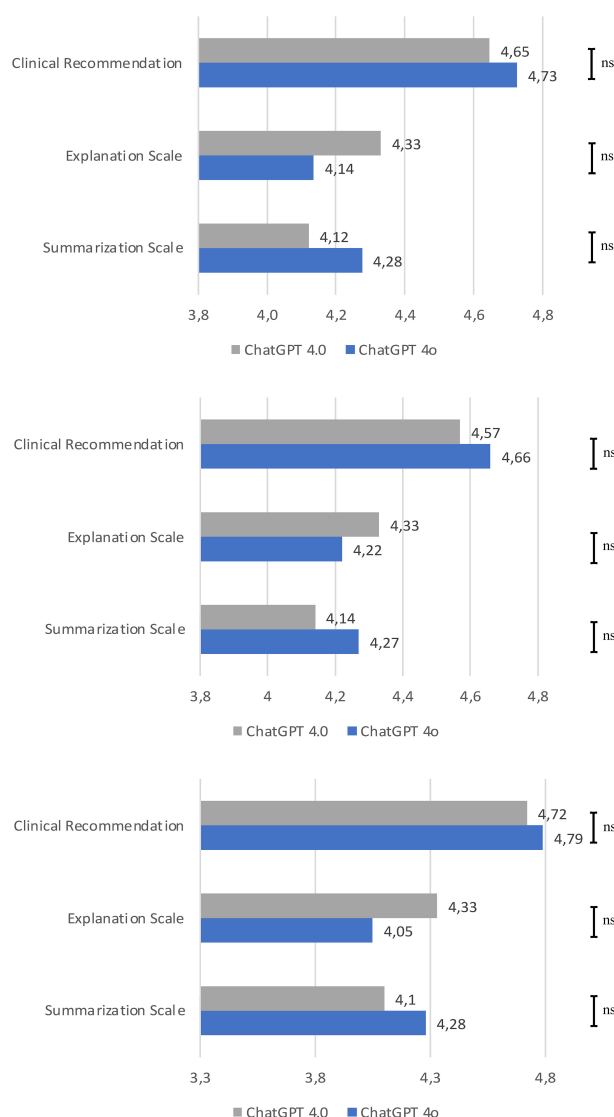


FIGURE 4

Rating of the performance of ChatGPT 4o and ChatGPT 4.0 by the grading of summarization of text, clinical recommendation, and explanation on the decision made by two independent reviewers. Overall result; Result of the metastatic cases; Result of the recurrent cases. Each bar is the average of the two independent reviewers grading. Statistical significance was calculated using the Mann-Whitney U Test. ns, non significant.

and have found applications across various medical specialties, including head and neck cancer, breast cancer, rheumatology, medical education, and many more (14, 17, 24–27) due to the ability to provide logical and appropriate responses to text questions through the application of advanced language modeling techniques and extensive access to large and diverse datasets (24, 25). Since MDTs have to consider a large quantity of data when reviewing a patient's case, including the clinical experience, as well as the most recent results of clinical and translational studies (9), LLMs could potentially organize and process data and thereby improve the workflow of clinical decision making. This was also the reason for the first studies investigating the use of AI for the MDT of HNSCC (6, 12, 13). These studies already demonstrated some of the challenges but also potential benefits of using AI for clinical decision making. These studies so far analyzed only a few select recurrent/metastatic HNSCC cases, in some studies even excluding

these cases. This study is therefore the first study involving only recurrent/metastatic HNSCC cases, with a total number of 100 patients enrolled. First of all, ChatGPT 4o demonstrated an improved efficiency in terms of processing time with a mean inference speed for ChatGPT 4.0 of 29.7 seconds (± 2.84), while ChatGPT 4o exhibited an improved mean inference speed of 20.0 seconds (± 5.33) can probably be attributed to optimizations in the model's processing capabilities (19). This is in line with OpenAI promising an up to 50% increased processing speed with ChatGPT 4o compared to ChatGPT 4.0 (28).

At the same time in this study, the performance of ChatGPT 4o was not significantly superior to ChatGPT 4.0 overall, achieving similar and convincing results in the grades of clinical recommendation, explanation, and summarization, with generally ChatGPT 4o being graded slightly better in terms of clinical recommendation, while ChatGPT 4.0 surpassed ChatGPT 4o in

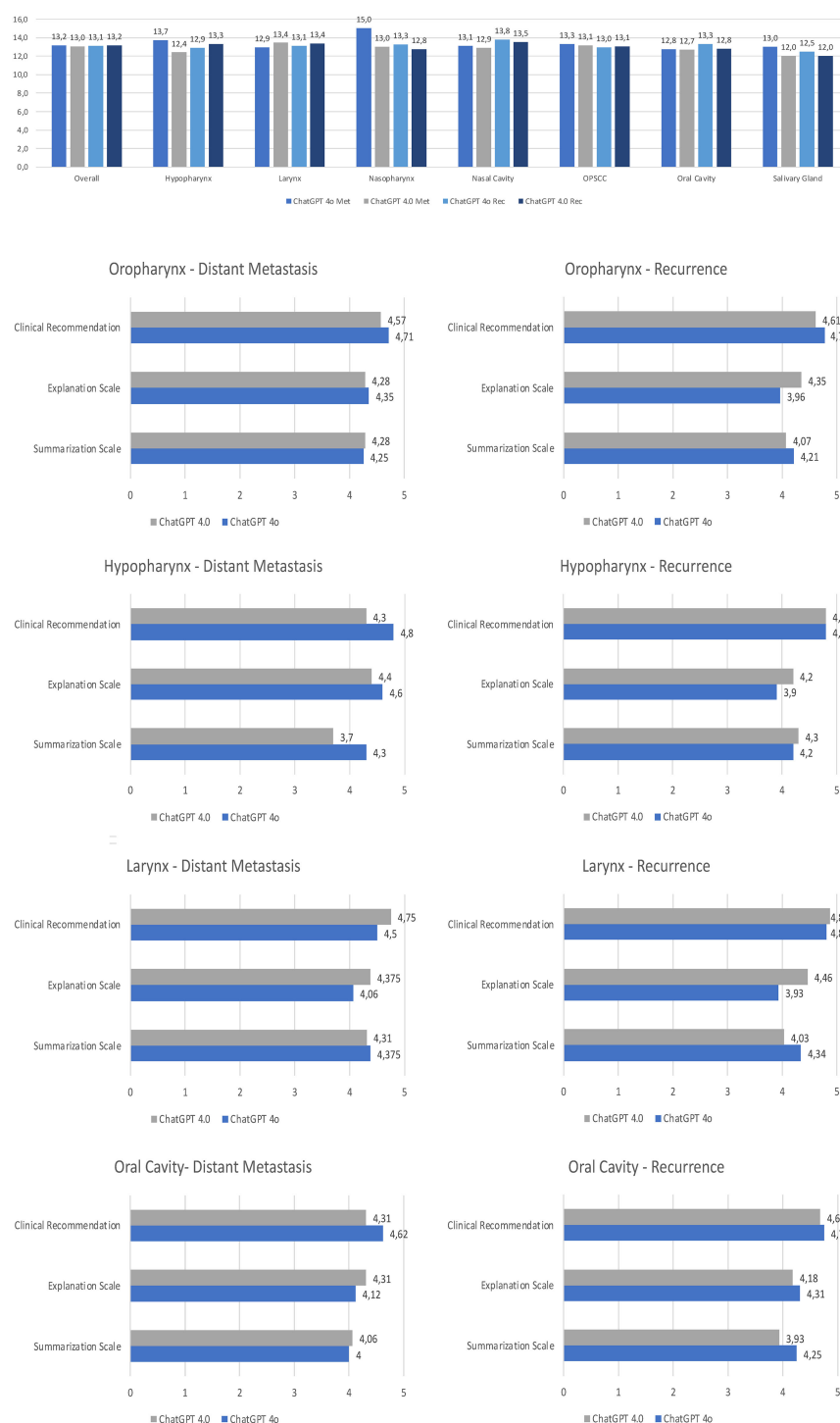


FIGURE 5

Rating of the performance of ChatGPT 4o and ChatGPT 4.0 according to the setting and the anatomical subsite. Total score of summarization, explanation and clinical recommendation; In depth results of the two LLMs for each subsite. Each bar is the sum of the grading of the two independent reviewers. Met, Metastatic situation; Rec, Recurrence; OPSCC, Oropharyngeal squamous cell carcinoma.

the grades of explanation and summarization. At the same time clinical recommendation was graded better for cases with distant metastasis compared to the cases with local/regional recurrence. While there have been no prior study investigating the use ChatGPT 4o for R/M HNSCC, the results of ChatGPT 4.0 are in line with different studies demonstrating an overall convincing

performance for oncological decision making, probably due to the ability to access more data than former studies using ChatGPT 3.5 (13, 17, 24). While ChatGPT was already able to access oncological data and provide accurate information about common cancer myths and misconceptions of the National Cancer Institute (29), the performance of more recent ChatGPT versions has not been

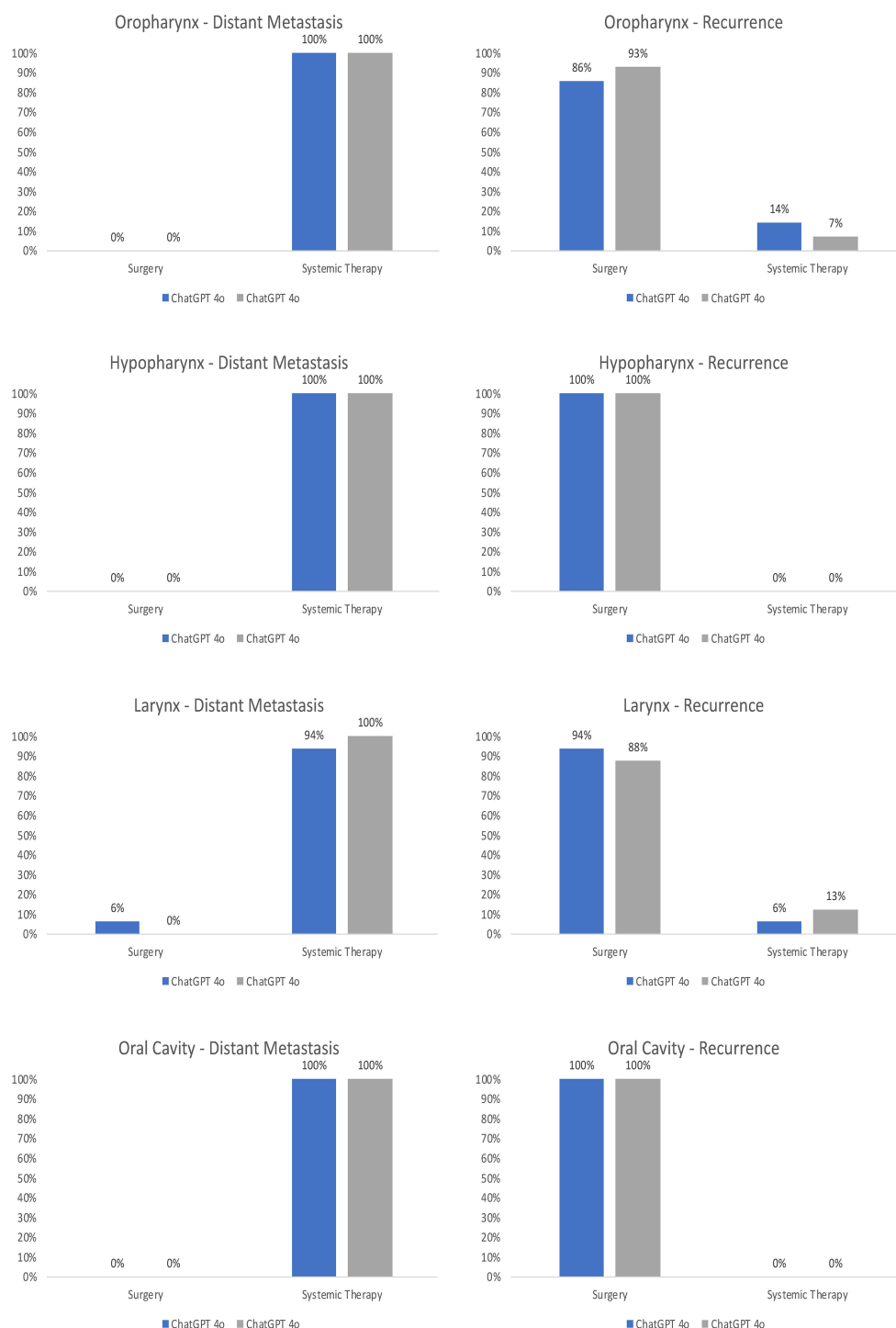


FIGURE 6

Anatomical subsites of the recommended treatment options of ChatGPT 4o compared to ChatGPT 4.0. The answers of both LLMs were evaluated by two independent reviewers for the first choice and second choice therapy recommendations in the recurrent and distant metastatic setting. The results were normalized to 100%.

studied extensively yet (19). According to OpenAI, ChatGPT 4o excels in understanding complex queries and improved contextual awareness, with new functions in the form of audio generation and image recognition (28). For the category of text evaluation the publisher itself lists some of the most commonly performed general benchmark tests, in which ChatGPT 4o reaches similar or slightly

improved scores (30). This could explain the results of this study with a similar performance of ChatGPT 4o in comparison to ChatGPT 4.0, since text evaluation might be the critical function of an LLM to assess the clinical setting of recurrent/metastatic HNSCC. Improvements in audio and visual recognition while significant in general applications, might not translate into

enhanced performance in the specific and complex environment of recurrent/metastatic HNSCC.

In the next step of this study the subgroups of recurrent and metastatic HNSCC were analyzed separately. The recurrent cases were graded slightly better in terms of clinical recommendation, while this was not significant. Overall, there was no statistically significant difference between both LLMs in the evaluation of recurrent/metastatic HNSCC cases. The in-depth analysis of the anatomical subsites reveals that the results for recurrent cancer of the oropharynx and larynx are the most divergent in terms of therapy recommendations and the performance results. This is probably due to the fact that these subsites are treated differently according to regional guidelines and the therapy is still controversially discussed, as seen in studies on de-escalation therapy of HPV-associated OPSCC or radiotherapy for early glottic cancer (29, 31). Unfortunately, it is currently not possible to investigate the source material leading to the therapy recommendations of the LLMs. While ChatGPT 4o is the latest version of OpenAI's highly performant LLM, and was introduced just a few weeks ago, the main advantages lie in the form of speed, image and audio recognition, cost efficiency, and lastly linguistic comprehension, in which it achieves a slightly better result than ChatGPT 4.0 and Claude 3 Opus (32). Since the MDT setting of recurrent/metastatic cases may not benefit from improvements in speed and linguistic comprehension, this might explain the similar results in this study compared to ChatGPT 4.0. Another potential explanation of the results of this study was the choice of the evaluation method. Even though the tool of Sorin et al. (21) was introduced for evaluating the MDT setting, and was used in different studies and clinical applications including primary HNSCC (12, 22), there are other tools such as the Artificial Intelligence Performance Instrument (AIPI) that have been validated more extensively (15). The AIPI is probably the most validated evaluation tool of ChatGPT so far but was designed primarily for evaluating the diagnostic performance of ChatGPT, containing 9 grades, of which only one grade (#9) evaluates the proposed treatment, therefore limiting the use in studies evaluating the performance of giving therapy recommendations in the MDT setting. Further studies are necessary to establish a validated performance tool in the MDT setting of HNSCC.

In terms of the therapy recommended for the 50 recurrent HNSCC patients, there is also only a slight discrepancy between the LLMs. Both LLMs recommended salvage surgery as the therapy with the best prognosis, and systemic therapy as the second choice. In cases with distant metastasis, systemic therapy was recommended, with a special focus on immunochemotherapy. While in a prior study of the use of ChatGPT 3.5 and 4.0 for the MDT of primary HNSCC (12) immunochemotherapy was falsely recommended for primary cases, this study demonstrated a more profound knowledge of the indication and approval by the FDA (33–35). Both LLMs are aware of the current guidelines of therapy in the R/M setting and explained the benefits and challenges of each therapy option in a mostly general way. Both LLMs were able to cite some of the most influential studies leading to the current guidelines. Early integration of palliative care was also mentioned

by both LLMs, especially by ChatGPT 4.0. This is especially important since head and neck cancer patients have complex palliative care needs and a high degree of symptom burden due to communication issues and other special needs (36). ChatGPT noted the importance of palliative care in the recurrent/metastatic setting of HNSCC, and already suggested many ways health care providers can support people in these difficult situations.

Other studies investigated clinical decision making with ChatGPT for ten consecutive patients with primary breast cancer and compared the treatment recommendations of ChatGPT 3.5 with the MDT and found similarities in 7 out of 10 cases (21). The interrater reliability in this study was similar to the results in our study, demonstrating that the evaluation of the performance of AI tools remains quite subjective. Compared to the results of our study of ChatGPT 4.0 and 4o, prior versions of ChatGPT achieved worse results in terms of decision making for head and neck cancer cases (13).

Since ChatGPT in our study explicitly states that it there has been no prior oncological training (37, 38), which limits the use for tailoring therapy guidelines to the specific needs of the individual patient, other research groups investigated the use of a clinical decision support system based on Bayesian networks (BN) for laryngeal cancer (LC) as a prototype with over 1,000 variables (39–41). In this approach, the TNM classification was the main classifier for the therapeutic recommendations, while ChatGPT 4.0 in this study is able to access an even larger database to address the comorbidities, extent of the tumor and some of the latest studies. Additionally, the software that was used has limited access, and investigated only data of laryngeal carcinoma without data on immunotherapy, therefore restricting the use as a clinical guidance tool in the recurrent/metastatic setting. On the other hand these models are more open and can be programmed and trained by physicians for specific clinical settings, such as the MDT of breast cancer (42), HNSCC (43), or for calculating the survival prognosis of patients (44). These custom programs are often technically demanding and need to be updated and modeled for each new setting, compared to the interactive and intuitive use of an LLMs for a variety of clinical applications without the need for additional programming. Once studies introduce new therapy options or change current guidelines, a Bayesian Network Model needs to be fully revised and trained (43). Since Bayesian Network Models have been trained and validated on medical data, while ChatGPT itself states that it has not received specific medical training, even though the datasets accessed by LLMs involve some of the most recent clinical studies and therefore suggest knowledge in these areas (45), the performance of an LLM for a specific clinical setting needs to be carefully evaluated in studies such as the one in this manuscript.

While the results indicating the quality of recommendations and evaluations for ChatGPT 4o and 4.0 in clinical practice are promising, both large language models have acknowledged certain limitations. Firstly, there is still a lack of transparency of the resources used to answer the prompts, also referred to as the black box of AI. It is unclear how most LLMs arrive at their decision, and it is therefore difficult to understand the rationale

behind specific decisions or predictions (46). Therefore, even if all of the recommendations are in line with the current guidelines, the results, must be evaluated carefully due to difficulties in reproduction and validation as seen also in other studies (10, 13, 38). Additionally, LLMs currently lack the level of contextual understanding necessary to customize advice to the unique situation of each patient, one of the most important aspects of personalized medicine and the MDT (12, 47). Patients with recurrent HNSCC often present with a distinct clinical history of previous treatments, genetic factors, and comorbidities. ChatGPT can assist the MDT by integrating patient-specific data with current medical literature and guidelines, but does not possess the ability of tailoring the treatment guidelines onto the specific patient. Without this ability, LLMs are limited to being an assistance and cannot replace the clinical experience of the members of the MDT (13).

Even though this study used a large cohort of 100 patients in the R/M setting, there is most likely a level of heterogeneity due to different anatomical subsites, historical and regional characteristics, which might influence the results of this study (6).

Another limitation is that every answer of an LLM depends heavily on the design of the prompt, with prompt engineering as a new discipline of developing and optimizing prompts to effectively utilize large language models (48). To address this issue, in this study different prompts were tested to find the most accurate prompt to generate convincing answers, while different prompt designs might lead to different responses (16, 25). Due to the potential influence of the prompt design on the performance of an LLM, there have been a few studies and position papers proposing strategies to standardize prompts (49). These prompt strategies include being specific, describing the setting to the LLM, and through testing and iteration (49). In this study the prompt was specifically designed to mirror the way a patient is presented at the MDT and was tested and iterated multiple times to overcome an insufficient performance of ChatGPT due to an error in the prompt design. For this study the same prompt was used both for ChatGPT 4.0 and 4o to allow a direct comparison of the performance in the HNSCC setting, whereas in future studies there might be different prompts for recurrent cases and cases with distant metastasis, since LLMs might need different prompt designs due to currently unknown reasons.

One of the main benefits of the MDT is the ability to discuss the patient's individual needs in a multidisciplinary setting and facilitate the tailoring of the therapy guidelines to the patient's situation. This is especially true for the recurrent/metastatic setting, in which the quality of life and the therapy options of a majority of patients are limited due to the side effects of prior radiation or surgical therapy (33, 50). Since LLMs are not able to think independently, generating output based on available public documents and databases (10), they do not possess the ability to tailor individual patient treatment plans. This emphasizes the importance of the MDT and the clinical experience of the health care provider, while the use of AI could potentially improve the efficiency and save time and resources in a period of time, in which the complexity and the number of clinical studies is steadily increasing. Another limitation of our study, is that HNSCC cases

of only one central European institution were investigated, whereas all MDTs are influenced by historical, local and personal reasons (7).

Overall, in this study ChatGPT 4o and 4.0 are able to produce convincing answers in terms of summarization, explanation and clinical recommendation for R/M HNSCC in this exploratory study. The performance in terms of overall speed, especially in the case of ChatGPT 4o, can help streamline the decision-making process by providing therapy suggestions and supporting information in seconds. The limitations of the current landscape of LLMs limit the clinical use in the MDT without supervision by an experienced clinician, but the knowledge of advanced LLMs in this study highlights the potential use in the future. Based on the results of this study, a prospective multicenter clinical trial and real-world validation are the next step to rigorously test AI models in the clinical setting of R/M HNSCC to provide robust evidence of their efficacy and safety, ultimately facilitating their integration into clinical practice. The areas of transparency, solid oncological training, as well as ethical concerns need to be addressed to overcome some of the current limitations. Nonetheless, the task of validation and the tailoring of the treatment to the patient will remain in the hands of the MDT and is based on the clinical knowledge of the clinical specialist.

5 Conclusions

In this exploratory study, the current version ChatGPT 4o and 4.0 demonstrated a profound knowledge of the indications and treatment options for recurrent and metastatic HNSCC, while there was no significant difference in the performance between both LLMs. Both LLMs achieved convincing grades for explanation, clinical recommendation, and summarization, while ChatGPT 4o was significantly faster than ChatGPT 4.0 in answering the prompts. The current limitations of LLMs demand careful validation and tailoring of the treatment before the implementation into the clinical setting of the MDT.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Technical University of Munich, 2024-184_1-S-NP. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

BS: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. ToH: Formal analysis, Methodology, Validation, Writing – review & editing. SP: Conceptualization, Data curation, Supervision, Validation, Writing – review & editing. FS: Data curation, Supervision, Validation, Writing – review & editing. CH: Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. TiH: Software, Supervision, Validation, Writing – review & editing. BW: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. MW: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

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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.2024.1455413/full#supplementary-material>

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Comparative study of CAD/CAM reconstruction and miniplates for patient-specific fixation in LCL-type mandibular reconstruction

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Objective: Miniplates offer superior clinical handling and facilitate postoperative removal after mandibular reconstruction but unfavorable load distribution under high stress has been shown. This study aimed to compare the clinical outcome of patient-specific 3D-printed (PS-3D) titanium miniplate with reconstruction plate fixation in three-segmental LCL-type reconstructions for the first time.

Methods: Patients undergoing three-segmental LCL-type mandibular reconstruction after malignant tumor resection between April 2017 and July 2023 were analyzed in a retrospective single-center study. Inclusion criteria were primary reconstruction using a fibula free flap and PS-3D titanium mini- or reconstruction plate fixation. Complication rates were recorded and analyzed within 6 months after surgery using the N – 1 Chi²- and unequal variance t-test.

Results: 38 patients (10 females, 28 males; mean age 61.4 ± 7.6 years) met the inclusion criteria. In 14 patients (36.8%) miniplates were used in the anterior region. Rates of fixation failure, plate exposure, incomplete osseous union, wound infection, soft tissue, and overall complications did not differ significantly between the two plate systems.

Conclusion: Complication rates did not differ significantly between PS-3D mini- and reconstruction plates in three-segmental LCL-type mandibular reconstructions. Given their advantages in clinical handling and postoperative removal, PS-3D miniplates can be a viable alternative also in larger mandibular reconstructions.

KEYWORDS

mandibular reconstruction, patient-specific, 3D-printing, titanium plate, miniplate, fibula flap, pseudarthrosis, CAD/CAM

1 Introduction

Mandibular segmental resection is the first-line treatment for oral carcinomas infiltrating the mandible (1). To restore chewing function, osseous free flap reconstruction followed by dental implant placement remains the gold standard (2). While superior to other reconstructive methods, post-operative complications remain, most notably osseous non-union, plate exposure and soft tissue complications (3, 4).

A significant risk factor for these complications are large mandibular defects, often requiring multi-segment flaps for reconstruction (5, 6). These extensive reconstructions necessitate a plate system capable of withstanding the increased mechanical stress of fixating multiple segments over a longer distance, while also promoting bone regeneration through beneficial strain (7, 8).

Recently, the use of patient-specific 3D-printed (PS-3D) plates has become increasingly common in mandibular reconstruction due to more predictable plate design and simplified surgical handling (9, 10). Nevertheless, plate-related complication rates have not improved significantly (4). In fact, the increased stiffness of PS-3D reconstruction plates is assumed to cause higher rates of osseous non-union (4, 11).

PS-3D miniplates were introduced by our group in 2022, to address some of the potentially complication-inducing properties of PS-3D reconstruction plates by allowing higher inter-osteotomy movements (IOM) and facilitating removability after surgery (8, 12, 13). Due to the reduced size of miniplates and the use of monocortical screws, plate removal can be performed via an intraoral approach in an outpatient setting with dental implantation in the same surgery resulting in significantly reduced treatment time and cost (12). In single-segment reconstructions, Ruf et al. demonstrated increased beneficial mechanical straining when using PS-3D miniplate fixation in the canine region over PS-3D reconstruction plate fixation (14). However, miniplates exhibited uneven load distribution when used for fixation at the mandibular angle, an area known to be associated with higher stress than the symphysis (15). To overcome this problem, a combined plate system for single-segment mandibular reconstructions using fibula free flaps was proposed: A shortened reconstruction plate at the mandibular angle and a pair of miniplates at the symphysis (16).

To date, this combined plate system has clinically only been evaluated for single- and two-segmental reconstructions where a tendency towards reduced complication rates compared to single PS-3D reconstruction plate fixation was registered (17). However, its behavior in high-stress LCL-type (18) reconstructions has not yet been evaluated clinically or biomechanically and is therefore of great interest.

We hypothesized that a combined PS-3D mini- and reconstruction plate osteosynthesis would not lead to increased complication rates compared to single reconstruction plate fixation

in three-segmental LCL-type mandibular reconstructions using fibula free flaps.

2 Methods

2.1 Study design

This retrospective single-center cohort study was designed at the department of Oral and Maxillofacial Surgery at Charité – Universitätsmedizin Berlin. Patients operated between April 2017 and July 2023 were deemed eligible for study enrollment. Follow-up documentation was analyzed until January 2024. Ethical approval was obtained from the local ethics committee (EA2/138/18).

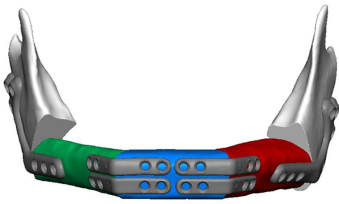
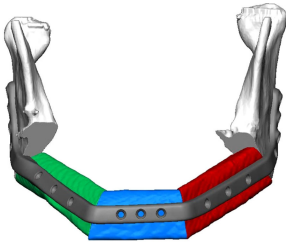
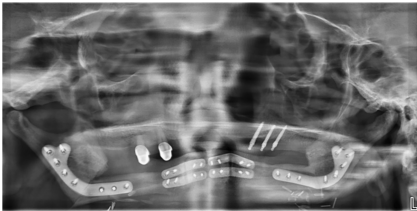
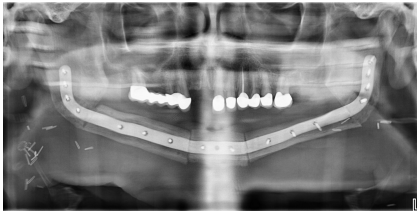
2.2 Inclusion and exclusion criteria

Inclusion criteria were fixation using a single PS-3D reconstruction plate bridging the entire three-segmental LCL-type defect or two shortened reconstruction plates at the mandibular angle in combination with PS-3D miniplates at the anterior region. Reconstructions involving the mandibular ramus were not included as biomechanical behavior and stress exhibited on the plates was assumed to differ significantly. The minimum follow up period was 6 months after surgery. To establish a homogenous cohort, only patients who received a fibula free flap as primary reconstruction following malignant tumor resection were included, as other common indication such as osteoradionecrosis are associated with poor clinical outcome themselves. We reviewed but excluded patients who suffered a flap loss within the follow-up period.

2.3 Procedures

The computer aided design/computer aided manufacturing (CAD/CAM) workflow of PS-3D plate design has previously been described in detail by our department (12, 17). All plates were manufactured by KLS Martin SE & Co. KG (Tuttlingen, Germany) using a titanium 3D-printing process. Reconstruction plates were designed with a thickness of 2.0 mm and height of 8.0 mm, mini plates with a thickness of 1.0 mm and height of 5.0 mm. Plate length was adjusted individually for each case. Miniplates were fixated with four 2.0 x 7.0 mm monocortical screws per plate, used in pairs at the corpus-symphysis intersegmental gaps and supported by two 6-hole reconstruction plates at the distal intersegmental gaps (Group 1) (Table 1). The reconstruction plates were fixated to the mandibular stumps using 2.0 mm bicortical screws while 7.0 mm monocortical screws were used for fixation of the free flap to protect the vascular pedicle (Group 2) (Table 1). For the first postoperative week, low molecular weight heparin (Fraxiparine 0.3 ml twice a day) was

TABLE 1 3D planning, clinical execution, and description of the two plate systems compared in this study.

Group 1: Reconstruction + miniplates	Group 2: Single reconstruction plate
	
	
Combination of short PS-3D reconstruction plates at the distal intersegmental gaps and PS-3D miniplates at the anterior intersegmental gaps	Single PS-3D reconstruction plate spanning all intersegmental gaps

PS-3D, patient-specific 3D-printed.

administered. Patients that received radiotherapy were treated according to the current German Cancer Guideline for Oral Cavity Cancer (1). The total dose administered was between approximately 70 Gy.

2.4 Data acquisition

All data was captured and managed using REDCap electronic data capture tools hosted at Charité – Universitätsmedizin Berlin (RRID: SCR_003445) (19, 20). Medical charts of all patients were screened for patient- and disease-related information: age at surgery, sex, body mass index (BMI), nicotine consumption, alcohol abuse, atherosclerosis, adjuvant radio- and chemotherapy. Information about the fixation system and use of an intraoral skin paddle was taken from the surgeon’s report. The follow-up documentation was screened for any of the predefined outcomes within a follow-up period of 6 months (Table 2). Radiographic images were taken 6 months after surgery and analyzed for osseous union.

2.5 Statistical analysis

Data engineering and statistical analysis was performed using the Python Programming Language version 3.11.5 (RRID: SCR_008394) and the Scipy Stats module (21–23). There was no missing data among predictor variables. Records with missing data in outcome variables were excluded in the respective analyses. Numeric variables were tested for normality using the Shapiro-Wilk-Test and analyzed for significant differences between the two plate groups using the unequal variance t-test (24). Nominal variables were tested for significance using the N - 1 Chi²-test as recommended by Campbell (25). Our study’s level of significance

was set at $p \leq 0.05$. In addition, inclusion of the null value in the 95%-confidence interval (CI) of an odds ratio (OR) was recorded as non-significant, while non-inclusion was recorded as significant.

3 Results

3.1 Patient inclusion process

355 patients were initially identified as eligible for study enrollment. Patients were excluded as per the previously

TABLE 2 Pre-defined diagnostic criteria for each outcome.

Outcome	Diagnostic criteria
Any complication	- any of the complications listed below
Fixation failure	- plate loosening - plate fracture
Plate exposure	- intraoral plate exposure - extraoral plate exposure
Incomplete osseous union	- ≥ 1 intersegmental gap with less than 50% radiographic ossification at least 6 months after surgery (diagnosed in CBCT, CT or OPT scans with decreasing priority)
Wound infection	- pus - infectious fistula - abscess formation
Soft tissue complication	- wound healing disorder - wound dehiscence - partial skin necrosis - plate exposure - bone exposure - wound infection (see criteria above)

CT, computer tomography; CBCT, cone-beam CT; OPT, panoramic radiograph. One fulfilled criterion sufficed to record the respective outcome.

described criteria. Of the remaining 39 patients, 1 (2.6%) patient belonging to the reconstruction plate group suffered a flap loss within the follow-up period. This case was excluded, resulting in a study population of 38 patients (Figure 1).

3.2 Baseline characteristics

The baseline characteristics of the study population are shown in (Table 3). All numeric variables were normally distributed. The patient collective was homogenous and differed significantly only in defect length between the two plate groups ($p = .038$): Patients who received the combined plate system had a mean defect length of 129.6 mm (± 17.3) while the other group had a slightly lower mean defect length of 113.5 mm (± 26.5). An intraoral skin paddle was used slightly less often with the combined plate system (42.9% vs. 66.7%, $p = .157$) while adjuvant chemotherapy was more common in the reconstruction plate group (50.0% vs. 28.6%, $p = .203$).

3.3 Bivariate analysis

Complication rates did not differ significantly between the two plate groups. One case of fixation failure occurred in the combined plates group due to a loosening of miniplates at the anterior mandibular segment. Imaging data from within the follow-up period was missing for 5 patients, resulting in a reduced number of cases analyzed for osseous union. Plate exposure occurred intraorally only (Table 4).

4 Discussion

This study is the first to analyze the postoperative outcome of PS-3D miniplate fixation in three-segmental LCL-type mandibular

reconstructions. We chose a combined system of two six-hole PS-3D reconstruction plates at both distal intersegmental gaps with PS-3D miniplates at the anterior gaps based on biomechanical findings by Ruf et al. (Figure 1) (14). This combined plate system had previously shown a tendency towards reduced complication rates in mandibular single- and two-segmental reconstructions and offers superior clinical handling when compared to single PS-3D reconstruction plate fixation (17).

Patient characteristics did not significantly differ between the two plate groups, except for defect length, which was longer in the combined plate group (129.6 ± 17.3 vs. 113.5 ± 29.3 mm, $p = .038$). While statistically significant, the absolute mean difference of 16.1 mm is relatively small and, if anything, may have slightly disadvantaged the new combined plate system due to the increased defect length.

In our study, the combined plate system was not inferior compared to single reconstruction plate fixation, as complication rates did not differ significantly. While higher fixation failure (7.1% vs. 0.0%, $p = .190$) and wound infection rates (50.0% vs. 25.0%, $p = .122$) were observed, this may be related to our study's limited sample size of 38 patients. It does not imply an inferiority of miniplates as the difference was not significant and may be related to randomness. However, further biomechanical and clinical analyses are recommended.

The present study's flap loss rate of 2.6% is lower than previously described rates ranging from 4.7% to 9.4%, although our follow-up time of 6 months was shorter than that of some other studies (3, 26). By only including patients who underwent fibula free flap reconstruction following malignant tumor resection, we avoided potential confounders arising from different flap types and surgical indications. This established a homogenous cohort of 38 patients which did not differ significantly between the two plate groups. An intraoral skin paddle was used slightly less often with the combined system (42.9% vs. 66.7%, $p = .157$). This difference is mainly due to our team's recent shift in operating technique,

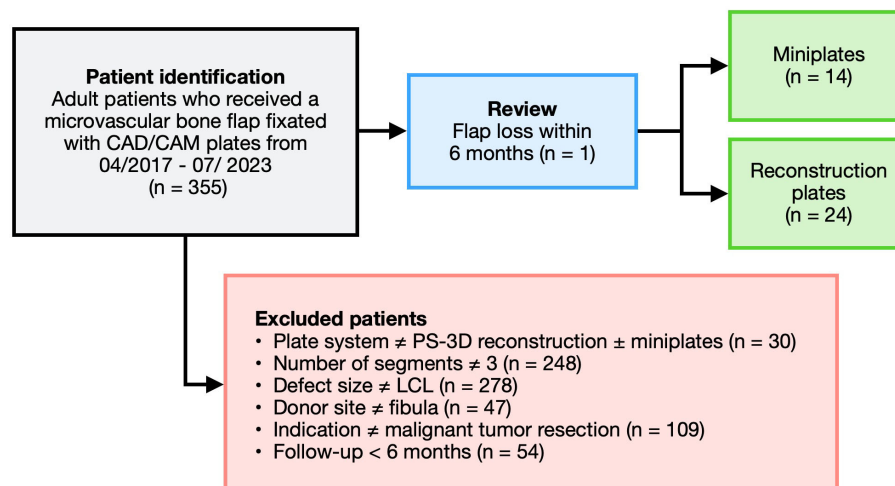


FIGURE 1
Visualization of the patient inclusion process.

TABLE 3 Baseline characteristics of the study population.

	Combined plates	Reconstruction plate	p-value	Overall
	n = 14 (36.8%)	n = 24 (63.2%)		N = 38 (100%)
Age (years)			.594	
Mean ± SD	60.6 ± 7.6	62.0 ± 7.8		61.4 ± 7.6
Sex			.606	
Female	3 (21.4)	7 (29.2)		10 (26.3)
Male	11 (78.6)	17 (70.8)		28 (73.7)
BMI (kg/m²)			.917	
Mean ± SD	23.7 ± 2.3	23.6 ± 4.7		23.6 ± 3.9
Nicotine abuse			.246	
Yes	6 (42.9)	15 (62.5)		21 (55.3)
No	8 (57.1)	9 (37.5)		17 (44.7)
Alcohol abuse			.581	
Yes	4 (28.6)	9 (37.5)		13 (34.2)
No	10 (71.4)	15 (62.5)		25 (65.8)
Atherosclerosis			.441	
Yes	2 (14.3)	6 (25.0)		8 (21.1)
No	12 (85.7)	18 (75.0)		30 (78.9)
Radiotherapy			.748	
Yes	8 (57.1)	15 (62.5)		23 (60.5)
No	6 (42.9)	9 (37.5)		15 (39.5)
Chemotherapy			.203	
Yes	4 (28.6)	12 (50.0)		16 (42.1)
No	10 (71.4)	12 (50.0)		22 (57.9)
Intraoral skin paddle			.157	
Yes	6 (42.9)	16 (66.7)		22 (57.9)
No	8 (57.1)	8 (33.3)		16 (42.1)
Defect length (mm)			.038	
Mean ± SD	129.6 ± 17.3	113.5 ± 29.3		119.4 ± 26.5

SD, standard deviation; BMI, Body Mass Index.

favoring the use of muscle tissue over a skin island to avoid a bulky soft tissue mass in the oral cavity. As miniplates were introduced later, a skin paddle was used less often in those surgeries.

4.1 Reconstruction versus miniplates

Several studies have previously compared conventional mini- and reconstruction plates, recently summarized in a meta-analysis by Sobti et al. (26). Their findings showed plate exposure and fixation failure rates to be significantly higher among conventional miniplates which contrasts with our findings showing no significant differences between PS-3D mini- and reconstruction plates (p = .260 and p = .190). However, their rates of 32.5% for

conventional mini- and 18.8% for conventional reconstruction plates were lower than our plate exposure rates of 42.9% and 25.0% for PS-3D mini- and reconstruction plates, respectively. This is in line with prior studies reporting on moderately increased complication rates for PS-3D plates (4, 27). While there was no case of extraoral plate exposure in the present study, the increased rate of intraoral plate exposure among miniplates can be attributed to a less frequent use of skin paddles by our team. In our experience, however, initial plate exposure of CAD/CAM miniplates typically does not lead to additional complications like osseous non-union or wound infection. Furthermore, this study did not compare conventional with PS-3D plates, and differences in complication definition and recording prevent cross-study comparisons.

TABLE 4 Results of bivariate analyses between the two plate systems and all outcomes.

	Combined plates	Reconstruction plate	p-value	OR [95%-CI]	Overall
	n = 14 (36.8%)	n = 24 (63.2%)			N = 38 (100%)
Any complication			.441	2.00 [0.34; 11.62]	
Yes	12 (85.7)	18 (75.0)			30 (78.9)
No	2 (14.3)	6 (25.0)			8 (21.1)
Fixation failure			.190	5.44 [0.21; 143.10]	
Yes	1 (7.1)	0 (0.0)			1 (2.6)
No	13 (92.9)	24 (100.0)			37 (97.4)
Plate exposure			.260	2.25 [0.55; 9.17]	
Yes	6 (42.9)	6 (25.0)			12 (31.6)
No	8 (57.1)	18 (75.0)			26 (68.4)
IOU overall			.510	1.62 [0.39; 6.68]	
Yes	9 (64.3)	10 (52.6)			19 (57.6)
No	5 (35.7)	9 (47.4)			14 (42.4)
Wound infection			.122	3.00 [0.74; 12.13]	
Yes	7 (50.0)	6 (25.0)			13 (34.2)
No	7 (50.0)	18 (75.0)			25 (65.8)
Soft tissue complication			.748	0.80 [0.21; 3.06]	
Yes	8 (57.1)	15 (62.5)			19 (57.6)
No	6 (42.9)	9 (37.5)			14 (42.4)

OR, odds ratio; CI, confidence interval; IOU, incomplete osseous union.

Ultimately, while complication rates seem to be significantly higher among conventional miniplates compared to conventional reconstruction plates, the same cannot be said for the combined system of PS-3D mini- and reconstruction plates analyzed in this study, as complication rates did not differ significantly compared to the reconstruction plate group. This is particularly beneficial since miniplates by design offer considerable advantages over reconstruction plates in clinical handling. Due to their reduced size, plate removal can be performed via an intraoral approach in an outpatient setting with dental implantation in the same surgery (28). This contrasts with reconstruction plate fixation, where achieving a similar outcome would often require intraoperative plate cutting and hospitalization, resulting in considerably higher costs (17).

4.2 Surgical handling of miniplates

The fixation failure rate of 2.6% remains lower than previously reported rates between 7.7% and 12.4% (3, 29). It resulted from one

case of plate loosening from the combined plate group, were both miniplate fixations at the anterior mandibular region loosened and were slightly dislocated. Our experience has shown that correct handling of miniplate fixation is highly relevant and can prevent post-operative plate loosening. Cutting guides need to be positioned with great precision and continuous additional rinsing during drilling is essential to prevent heat damage in the drilling holes. We further recommend pre-fixation of all plates at the harvesting side prior to vessel ligation without fully tightening any screw. Only once the 3-segmental fibula free flap can be placed in the desired position between the residual mandibular stumps without putting stress on plates or screws should the three posterior screws be inserted in the mandibular stump on each side and all other screws fixated definitively. Compression with 2 hands from the lateral side during anterior screw fixation is sometimes necessary to avoid rotation and consequently mispositioning of the segments. Only a very thin muscle cuff and periosteum should remain on top of the lateral fibula during flap harvesting to enable sufficient miniplate fixation with mono-cortical screws in a load-sharing manner

through frictional loading between the fibula segments and fixation plates.

4.3 Bone healing

Bone regeneration is essential to prevent osseous non-union but has been shown to be sensitive to suboptimal mechanical conditions (30, 31). Unfavorable inter-osteotomy movements (IOMs) due to inadequate load distribution may therefore lead to an incomplete osseous union, in turn resulting in chronic overload on the osteosynthesis material. This can potentially lead to fixation failure, especially if patients regain their full bite force. Despite theoretical advantages of PS-3D miniplates in bone regeneration in single-segment reconstructions (14), the present clinical study revealed no difference in osseous non-union rates compared to PS-3D reconstruction plate fixations (64.3% vs. 52.6%, $p = .510$) in LCL-type reconstructions. While our observed rates are in line with studies by Knitschke et al. for conventional and PS-3D reconstruction plates (27, 29), Kreutzer et al. found a significantly reduced osseous non-union rate for the combined plate system in single- and two-segmental reconstructions (6.7% vs. 46.2%, $p = .029$) (17). Given that LCL-type reconstructions usually result in postoperative toothlessness and thus permanently reduced bite forces, miniplates would have been assumed to be particularly beneficial in such low-stress scenarios as this has been shown to result in increased beneficial straining in single-segment reconstructions (14). High rates of incomplete osseous union for miniplate fixations, as seen in the present study, are therefore unexpected but may be related to the increased instability of three-segmental LCL reconstructions. Whether a load-bearing reconstruction plate is beneficial due to its rigid fixation remains to be investigated by future biomechanical studies, as such an effect could not be proven in the present clinical study.

Nevertheless, it should not be overlooked that patients requiring LCL-type reconstructions due to malignant tumors are more likely to also receive adjuvant radiotherapy, a known risk factor inhibiting osseous union (27). Furthermore, we screened patients for osseous union 6 months after surgery, limiting comparability to other studies with a longer follow-up period, as Knitschke et al. have shown osseous union rates to improve considerably over time (27). Further biomechanical studies employing bite force analyses are needed to analyze how mechanical strains in LCL-type reconstructions can be improved. Existing biomechanical analyses, focused only on single-segment reconstructions, may not accurately reflect the mechanical stresses present in more extensive defects (32).

4.4 Study limitations

Our study is associated with some limitations that should be mentioned. While our focus on a homogenous cohort strengthens the internal validity of our findings, it comes at the cost of excluding other relevant surgical indications such as osteoradionecrosis and flaps other than fibula free flaps. Additionally, three-segmental LC-

type reconstructions and those including the mandibular ramus were excluded from the present study, as these reconstructions are assumed to differ substantially from the studied LCL-type reconstructions regarding the mechanical stress exhibited on plate system and transplant. We chose a follow-up time of 6 months as most complications tend to occur within this time frame and relatively few patients had to be excluded due to an incomplete follow-up. However, long-term complications occurring later than 6 months post-surgery were not captured and should be evaluated in future studies. Ultimately, our study's retrospective design comes with inherent limitations, only allowing limited generalization of the results.

5 Conclusion

Our study found no significant differences in complication rates between PS-3D mini- and reconstruction plates. Given the established benefit of easier postsurgical miniplate removal in the anterior mandibular region, clinical superiority over single PS-3D reconstruction plate fixation can be inferred. Further research is needed to understand load distribution and failure mechanisms specifically in multi-segment mandibular reconstructions, as biomechanical conditions may differ considerably from single-segment reconstructions. Perioperative functional analyses can thereby help identify strategies to improve osseous healing in large mandibular reconstructions.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the ethics committee of Charité - Universitätsmedizin Berlin. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PL: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. JF: Investigation, Writing – review & editing. JW: Writing – review & editing, Resources. SK: Resources, Writing – review & editing. KK: Writing – review & editing, Resources. PR: Validation, Writing – review & editing. SC: Writing – review & editing, Validation. MH: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing. CS: Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. CR:

Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

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Case report: Microsurgical resection of a giant triple dumbbell shaped jugular foramen Schwannoma via retrosigmoid and transcervical approach

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The surgical management of extensive jugular foramen schwannomas presents a formidable challenge, aiming for gross total resection while minimizing complications. Here, we present a case with giant triple dumbbell-shaped jugular Foramen Schwannoma. A 45-year-old male with a one-year history of a left neck mass underwent surgery. Initial misdiagnosis of submandibular gland inflammation led to persistent symptoms despite anti-inflammatory treatment. Imaging revealed a large lesion in the left cerebellar peduncle-neck-jugular foramen region (39.6 x 26.2 x 90 mm). The combination of retrosigmoid and transcervical approach was selected. Sufficient drilling of the infralabyrinthine, retrofacial area of the mastoid with facial nerve transposition is important for the safe gross total removal of the tumor. The patient underwent a gross total removal of the tumor. Facial nerve function was preserved. Although dysphagia and hoarseness complicated postoperatively, he became able to take foods orally after the surgery. In conclusion, this case underscores the successful surgical approach for a large jugular foramen Schwannoma, emphasizing the importance of precise techniques to achieve complete tumor resection while minimizing postoperative complications.

KEYWORDS

jugular foramen, Schwannoma, microsurgery, transmastoid, triple dumbbell-shape

Introduction

Jugular Foramen Schwannomas (JFSs) is a rare and challenging condition characterized by the presence of schwannomas in the jugular foramen, an anatomically complex region of the skull (1, 2). The jugular foramen region encompasses critical neurovascular structures, including the lower cranial nerves and jugular vein (3). JFSs constitute approximately 2.9–4% of all

intracranial schwannomas (4). Despite its low incidence, the surgical management of extensive JFSs remains a formidable challenge due to the intricate anatomy and potential for complications. JFSs are classified based on their shape and extension. Samii's classification categorizes JFSs into three subtypes based on tumor location and extensions: type A (tumors mainly in the cerebellopontine angle with jugular foramen enlargement), type B (tumors primarily in the foramen with intracranial extension), and type C (mainly extracranial tumors extending into the jugular foramen, forming dumbbell-shaped tumors across intracranial, jugular foramen, and extracranial compartments) (5, 6).

Attaining total resection of tumors in this area necessitates an optimal neurosurgical approach. Several approaches, such as the far lateral approach, juxtacondylar approach, and postauricular transtemporal approach, have been introduced in alignment with this classification (7). For extensive dumbbell-shaped JFS, a two-piece lateral suboccipital approach emerges as a suitable option (8). The surgical approach to these tumors is critical for achieving gross total resection while preserving vital structures and minimizing postoperative complications. Common complications associated with these tumors include facial nerve paresis, hearing disturbances, dysphagia, hoarseness, and cerebrospinal fluid (CSF) leakage, emphasizing the need for precise surgical techniques (9).

Within this context, we present the case of a 45-year-old male diagnosed with a rare giant triple dumbbell-shaped jugular foramen Schwannoma. The patient's clinical history, initial misdiagnosis, diagnostic imaging, and the selected surgical approach bring attention to the intricacies and considerations inherent in managing such uncommon tumors. This case not only enhances our understanding of the diverse presentations of jugular foramen Schwannomas but also underscores the crucial role of personalized surgical strategies. The favorable outcome, marked by preserved facial nerve function and improved postoperative conditions, highlights the critical importance of detailed surgical planning

and precise execution to achieve optimal results in patients grappling with this challenging condition.

Case presentation

Clinical history

This case report has been prepared in accordance with the CARE (Case Reports) guidelines, as available on the EQUATOR Network (<https://www.equator-network.org/>). A 45-years-old male presents to Wuhan Union hospital complaining of a mess on the left side of the neck over the past year. A neck ultrasound conducted at a local hospital one year ago revealed a 5*4*2 cm mass on the left side of the neck. No specific treatment was administered at that time. About half year later, a repeat neck ultrasound indicated no significant change in the size of the mess. A subsequent biopsy suggested the possibility of submandibular gland inflammation. The patient received anti-inflammatory treatment, but the response was unsatisfactory. Over the past three months, the patient has experienced dizziness without presenting symptoms such as hoarseness, hearing loss, facial paralysis, or difficulty swallowing. Seeking further evaluation and treatment, the patient visited our outpatient clinic. A new audiological assessment was performed and revealed no difference in hearing between the left and right ears (Figures 1A, B).

Imaging

Computed tomography imaging

In the left cerebellar peduncle-neck-internal aspect of the jugular foramen region, there is a longitudinally shaped lesion with mixed long T1 and long T2 signal, showing a clear border and extending medially to the left para-pharyngeal space. The lesion exhibits significant and

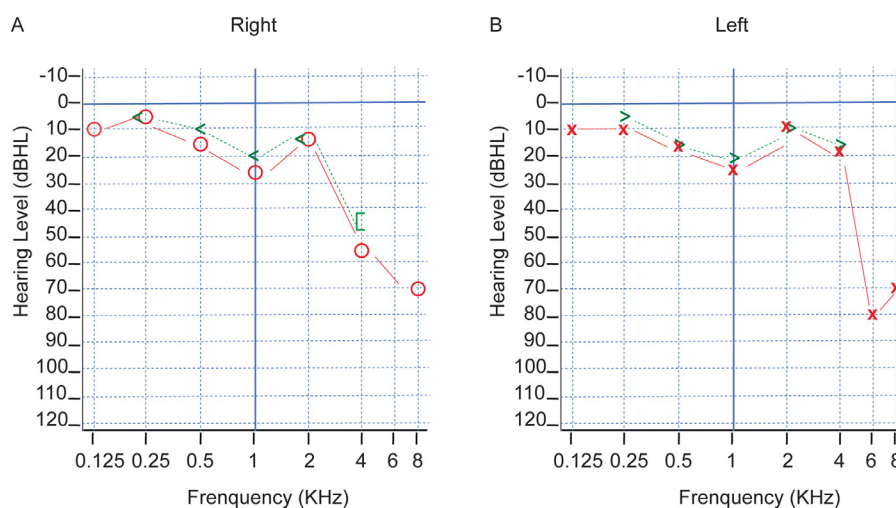


FIGURE 1

(A, B) Pure tone audiometry results. Preoperative hearing audiogram shows no difference in hearing between the left and right ears. Both ears demonstrate severe high frequency sensorineural hearing loss. Symbols: O, right ear air conduction; <, left ear bone conduction; X, left ear air conduction; >, left ear bone conduction. dBHL, decibels Hearing Level; KHZ, kilohertz.

uneven enhancement on contrast imaging, with compression and flattening of the surrounding jugular veins and no obvious contrast agent filling. The lesion measures approximately 39.6 x 26.2 x 90 mm (Figures 2A-C). Based on CT scans, Radiant DICOM viewer software (version 2024.1, Germany) was applied to reconstruct the three-dimensional model to demonstrate the spatial relationship of the tumor, arteries, head, and neck (Figures 2D-I). Both external ear canals are normal. No obvious abnormal high or low-density signals are observed within the middle ear cavity and mastoid air cells. The ossicles on both sides show no apparent abnormalities. Additionally, there are no apparent abnormalities detected in the inner ear and internal auditory canal on both sides (Figures 2J-L).

Magnetic resonance imaging

In the left pontocerebellar junction - jugular foramen, there is a mass with mixed long T1 and long T2 signals on the inner side of the neck vessel sheath. The mass has a clear border and extends inward to the left parapharyngeal space. It shows significant and uneven enhancement, measuring approximately 40*26*90mm. On the lesion plane, the left internal and external carotid arteries are displaced outward, and there is no apparent contrast agent filling in the local internal jugular vein (Figures 3A-C).

DSA with arterial injection of non-ionic iodinated contrast agent was performed in the left and right carotid arteries, as well as the left vertebral artery. The angiography revealed no apparent

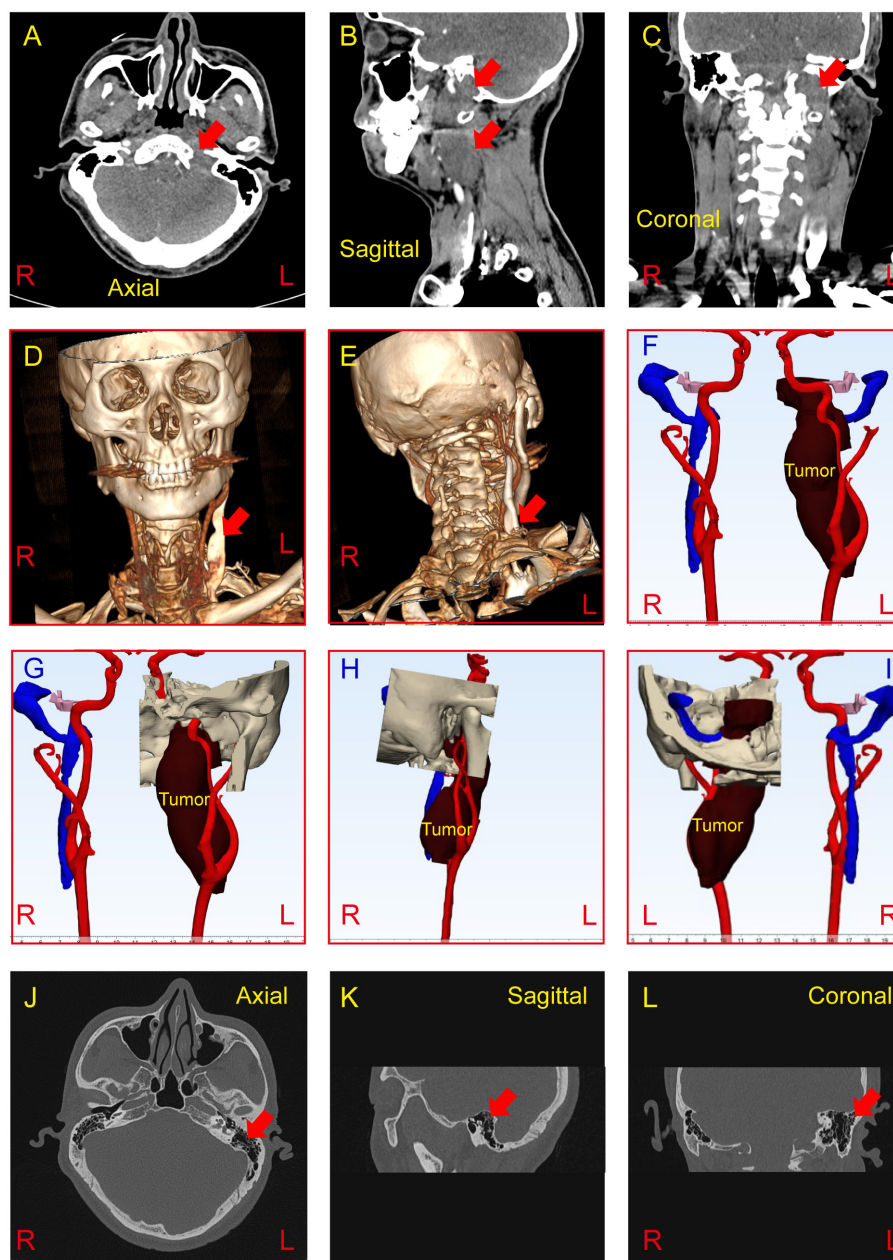


FIGURE 2

(A-C) CT imaging reveals an abnormal density mass in the left cerebellopontine angle, jugular foramen, and retrostyloid space, demonstrating mild to moderate heterogeneous enhancement (Red arrow). The tumor measures approximately 37*20*87mm. (D-I) Three-dimensional tumor model was reconstructed based on preoperative CT scan to show the spatial relationship of the tumor, arteries, and veins. (J-L) CT findings demonstrate no abnormalities in the bilateral external ear, middle ear, and inner ear (Red arrow show the left mastoid). R, Right; L, Left.

abnormal staining in the left neck to intracranial region. Arterial course and morphology were normal, and no obvious abnormalities were observed. The distribution of various draining veins showed a generally normal pattern (Figures 3D–F).

Surgery

A C-shaped postauricular skin incision is made. It begins at the upper edge of the auricle, curves 4 to 5 cm behind the postauricular sulcus, and slants inferiorly to end the lower border of the sternocleidomastoid muscle (Supplementary Figure S1A). User Grinding away the cortical and mastoid air cells of the mastoid, exposing the jugular foramen area, excising the mass in the jugular foramen area, and separating the tumor, vessels, and nerves downward. Dissecting the tumor from the dura mater and the overlying bony plate, grinding off the posterior cranial fossa bony plate, incising the dura mater, exposing the mass, and gradually performing intracapsular excision of the mass. Noting the convergence of the posterior cranial nerves into the mass and completely peeling off the mass (Supplementary Figures S1B–E).

Pathological examination

The conclusive histopathologic examination definitively established the diagnosis of Schwannoma, as depicted in Figures 4A, B. The immunohistochemical analysis of the tumor further substantiated the diagnosis, demonstrating positive staining for S100, SOX10, and CD34 (Figures 4C–E). Notably, the tumor exhibited negative immunoreactivity for GLUT1 and EMA (Figures 4F, G). Additionally,

the proliferation index, as indicated by Ki67, was notably low at 1% (Figure 4H), providing evidence of the tumor's limited proliferative activity. These findings collectively support the accurate identification of the lesion as Schwannoma and provide a comprehensive immunohistochemical profile for further characterization.

Post-surgery magnetic resonance imaging

The patient underwent a follow-up MRI seven months post-surgery, which revealed the following: the soft tissue on the left side of the neck was thinner compared to the right side (Supplementary Figures S2A–C). A mixed signal was observed in the left jugular foramen area, with a small amount of unevenly enhanced solid components (Supplementary Figures S2A–F). However, no evidence of tumor recurrence was detected.

Discussion

The presented case of a giant triple dumbbell-shaped jugular foramen Schwannoma underscores the intricate nature of surgical management and the importance of tailored strategies for optimal outcomes. Jugular Foramen Schwannomas (JFSs) are rare, constituting approximately 2.9–4% of all intracranial schwannomas, and pose significant challenges due to their location and potential complications (7).

Existing literature on JFSs, including studies such as those by Takahashi M et al., Bakar B. et al., and others (10–13), provides valuable insights into the classification, surgical management, and outcomes of these tumors. Samii's classification categorizes JFSs into

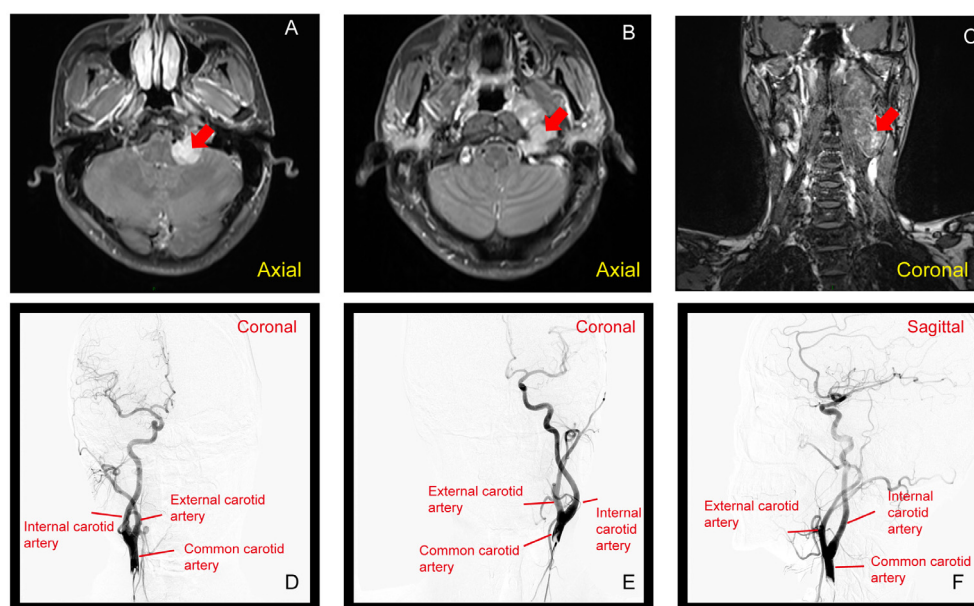


FIGURE 3

(A–C) MRI showing a mass at the left pontocerebellar junction to the jugular foramen, with mixed long T1 and T2 signals. The mass, measuring 40×26×90 mm, shows uneven enhancement (Red arrow show). (D–F) DSA with arterial injection of non-ionic iodinated contrast agent in the left and right carotid arteries, and left vertebral artery. The angiography shows no abnormal staining from the left neck to the intracranial region, with normal arterial course and morphology. The distribution of draining veins appears generally normal.

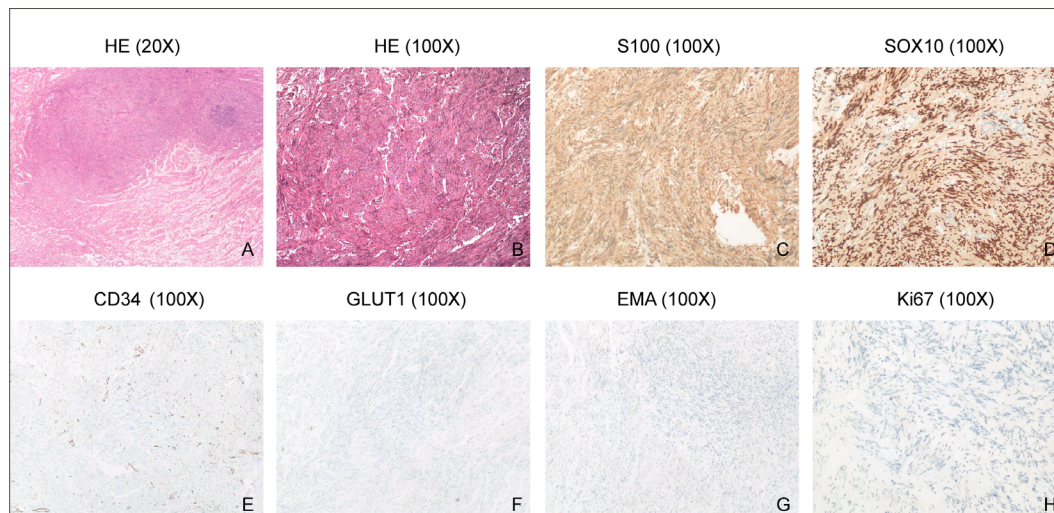


FIGURE 4

H&E staining and Immunohistochemistry. (A, B), HE staining shows spindle-shaped schwannoma cells. (C–G), Immunohistochemical analysis demonstrates positive staining for S100, SOX10 and CD34 in the tumor, but negative staining for GLUT1 and EMA. (H), Ki67 immunostaining reveals a low proliferation index of 1% in the tumor, indicating a relatively low rate of cell proliferation.

three subtypes (type A, B, and C) based on their shape and extension (5). However, the complexity of cases within each subtype often necessitates tailored approaches. For instance, type C tumors, which involve extensive extracranial and intracranial extensions, require particularly nuanced surgical planning. The literature also highlights various surgical approaches, with retrosigmoid and transcranial routes being commonly employed based on tumor location and extent.

Despite these advances, the treatment of JFSs remains challenging, with case series often reporting a balance between achieving gross total resection and minimizing neurological deficits. Recent studies have emphasized the importance of intraoperative neuromonitoring and advanced imaging techniques in improving surgical outcomes, yet each case presents unique anatomical and pathological considerations that must be addressed individually (14, 15).

Our case falls within the type C category, involving a mainly extracranial tumor extending into the jugular foramen, forming a dumbbell-shaped tumor across intracranial, jugular foramen, and extracranial compartments (4, 14). The tumor's extensive involvement required a combination of retrosigmoid and transcranial approaches, with a key innovation being the preservation of the facial nerve without transposition. This approach, not commonly highlighted in the literature, was critical in maintaining facial nerve function, as evidenced by the patient's postoperative recovery.

Furthermore, the precise drilling technique employed in the infralabyrinthine, retrofacial area of the mastoid, without compromising the facial nerve, represents a significant surgical advancement. The use of intraoperative neuromonitoring throughout the procedure further ensured the safety of the patient.

Precise surgical planning and execution are paramount, given the involvement of critical neurovascular structures. The successful gross total removal of the tumor in our case, despite the initial misdiagnosis and challenges posed by the extensive nature of the Schwannoma, highlights the effectiveness of the chosen surgical approach. Notably, meticulous drilling of the infralabyrinthine,

retrofacial area of the mastoid without facial nerve transposition played a crucial role in ensuring both safety and efficacy.

Postoperatively, the patient experienced complications such as dysphagia and hoarseness. However, these transient issues were outweighed by the overall success of the surgery, as the patient regained the ability to take foods orally, and facial nerve function was preserved. These outcomes underscore the importance of weighing potential complications against the benefits of tumor resection.

The pathological examination confirmed the diagnosis of Schwannoma, with immunohistochemical analysis providing valuable insights into the tumor's characteristics. Positive staining for S100, SOX10, and CD34, coupled with low Ki67 proliferation index, aligns with typical Schwannoma profiles. The negative immunoreactivity for GLUT1 and EMA further supports the accurate identification of the lesion.

In cases of residual or recurrent tumors, stereotactic radiosurgery offers a viable adjunctive treatment. Gamma Knife radiosurgery is particularly effective for lesions extending down to the C3 vertebra. For lesions adjacent to critical neural structures, fractionated radiosurgery may be indicated to minimize damage to surrounding tissues. Additionally, the incorporation of radioenhancers can potentiate the therapeutic dose to the tumor while sparing normal tissues (16, 17). These advanced techniques broaden the scope of effective management options for complex JFSs.

In conclusion, while the literature provides a foundation for understanding the complexities of JFS management, this case contributes a unique perspective on the surgical treatment of giant triple dumbbell-shaped tumors. The innovative approach, particularly in preserving facial nerve function without transposition, alongside the meticulous pre-operative planning and execution, adds significant value to the current body of knowledge. This case not only underscores the importance of individualized surgical strategies but also highlights the potential for improved outcomes through careful application of advanced techniques and technologies in complex JFS cases.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

Ethics statement

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

HS: Formal analysis, Funding acquisition, Writing – original draft. YH: Writing – original draft. YZ: Methodology, Software, Writing – original draft. JH: Writing – original draft. JY: Methodology, Resources, Software, Writing – original draft. ZH: Data curation, Funding acquisition, Investigation, Supervision, Validation, Visualization, Writing – review & editing. HC: Data curation, Investigation, Supervision, Validation, Visualization, Writing – review & 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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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2024.1432835/full#supplementary-material>

SUPPLEMENTARY FIGURE 1

Intraoperative images. (A) Surgical incision starting from behind the ear, extending posteriorly, progressing to the neck, and terminating at the inferior border of the sternocleidomastoid muscle. (B) Excised mass during the surgery. (C, D) Intraoperative visualization revealing tumor infiltration into the intracranial space with associated skull base damage. (E, F) Intraoperative observation highlighting the close relationship of the tumor with vascular and neural structures. IAA: internal auditory nerve; FN: Facial nerve.

SUPPLEMENTARY FIGURE 2

Postoperative enhanced MRI. (A–C) T1-enhanced sequences show that the soft tissues in the left neck are thinner compared to the contralateral side (Red asterisk). (A–F) T1-enhanced sequences also demonstrate heterogeneous signal intensity in the left jugular foramen area, demonstrating slight uneven enhancement with a solid component (Red arrow head).

SUPPLEMENTARY VIDEO 1

The external auditory canal is closed to prevent any potential complications. The cortical and mastoid air cells are ground away, revealing the jugular foramen area. The mass in the jugular foramen is excised, with the tumor, vessels, and nerves dissected downward. The tumor is carefully separated from the dura mater and underlying bone, and the posterior cranial fossa bony plate is removed. Following the incision of the dura mater, the mass is exposed and an intracapsular excision is performed. The posterior cranial nerves converging into the mass are identified and the mass is fully excised.

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Patient-reported quality of life and adherence outcomes after integrating exclusive liquid meal replacement in patients with head and neck cancer undergoing chemoradiation: results from a phase II study

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Objectives: Preventing malnutrition during chemoradiation (CRT) for head and neck cancer is critical maximizing quality of life (QOL). We sought to assess patient-reported QOL outcomes after integrating exclusive liquid meal replacement with Soylent, a novel meal replacement agent, in patients with head and neck cancer undergoing CRT.

Methods: Patients undergoing definitive or adjuvant concurrent CRT for locally advanced head and neck cancer enrolled on our single-institution, prospective phase II protocol evaluating nutritional replacement with Soylent. Patients who reached 5% body weight loss during CRT were transitioned to Soylent meal replacement for all nutritional needs. Patients who reached 10% body weight loss were recommended for gastrostomy tube (G-tube) placement. UW-QOL and FACT-H&N questionnaires assessed patient-reported QOL prior to the receipt of CRT and following conclusion of CRT. Paired t-test or Wilcoxon signed-rank test were performed to assess for differences between scores at each follow-up time point and baseline.

Results: Of the 60 enrolled patients, 51/60 (85%) lost 5% of their pre-treatment body weight. Among these patients, 48/51 (94%) were successfully transitioned to Soylent. 22/48 patients subsequently lost 10% of their pre-treatment body weight, and 3/22 (14%) underwent G-tube placement with the remainder declining. This resulted in an overall G-tube rate of 5%. Among the 41 patients evaluable for QOL data, the nadirs for overall and health-related UW-QOL were reached at 1 month and rebounded to exceed baseline by 6 months. FACT-H&N survey scores were reduced from 32 at baseline to 20 at 1 month (adjusted

$p < 0.001$) and 26 at 3 months (adjusted $p < 0.001$), but increased to 29, 30, and 27 at 6, 12, and 18 months, without significant differences as compared to baseline (adjusted $p > 0.38$ for all).

Conclusions: We report high patient adherence and a 5% G-tube placement rate with exclusive meal replacement with Soylent in patients undergoing concurrent CRT for head and neck cancers.

KEYWORDS

head and neck cancer, chemoradiation, nutrition, gastrostomy tube, quality of life

Introduction

Concurrent chemoradiation (CRT) remains a curative, standard of care treatment for malignancies of the head and neck, both in the definitive and adjuvant setting. However, this treatment has been historically associated with significant short and long-term toxicities including mucositis, xerostomia, dysgeusia, dysphagia, nausea, and vomiting, and malnutrition (1).

Maintaining adequate nutrition to minimize weight loss during CRT for head and neck cancer is crucial for minimizing short and long-term treatment-related complications as well as maximizing treatment adherence, patient-reported quality of life (QOL), and cancer-related outcomes (2, 3). Oral nutritional supplementation is a common strategy for nutritional maintenance, though adherence can be challenging due to taste fatigue and treatment-related sequelae (4). If nutritional needs continue to be unmet, placement of a gastrostomy tube (G-tube) represents an invasive but often necessary escalation in the management of head and neck cancer patients undergoing CRT in order to ensure nutritional maintenance. While this strategy is reliable for enhancing nutrition, long-term swallowing dysfunction may increase when patients rely on G-tube feedings, leading to higher rates of permanent G-tube dependence (5, 6). Even in the modern treatment era, a recently published randomized de-escalation study of cetuximab vs cisplatin for human papilloma virus (HPV) positive oropharyngeal cancer (RTOG 1016) reported G-tube placement rates of 61.5% at treatment completion in the cisplatin arm which translated to a 9.2% G-tube placement rate at 1 year following treatment (7). Rates were nearly identical (57.3% and 8.4%) on the cetuximab arm. Strategies to maintain adequate nutrition during non-de-escalated CRT while simultaneously reducing G-tube dependence are thus desperately needed.

Soylent is a widely available meal replacement beverage that was designed to entirely fulfill human nutritional needs (8). It represents an attractive meal replacement solution for head and neck cancer patients owing to its taste fatigue-reducing formulation and comprehensive nutritional profile.

We sought to assess the compliance and QOL outcomes associated with complete nutritional replacement with Soylent in patients who experienced 5% weight loss during CRT. We hypothesized that meal replacement with Soylent would be well tolerated and would improve nutritional status, thereby reducing the historic rate of therapeutic G-tube insertion at our institution (30%) as well as the overall rate of G-tube placement on contemporary studies of head and neck cancer (61.5%).

Methods

From August 2018 to March 2020, a total of 60 patients undergoing CRT for head and neck cancer were enrolled on a phase 2 single-institution trial of exclusive meal replacement with Soylent conducted at The University of California Los Angeles. Patients referred to radiation oncology for receipt of chemoradiation therapy were recruited to participate in the study by physicians in radiation oncology during their initial consultation visit.

Patients eligible for enrollment were required to have locally advanced head and neck malignancies for which CRT was recommended for definitive or adjuvant treatment. All radiotherapy was delivered using IMRT and conventional fractionation. Systemic therapy was delivered intravenously under the supervision of a medical oncologist. Patients were required to be ≥ 18 years of age with a Karnofsky Performance Status (KPS) ≥ 70 , a body mass index (BMI) $\geq 18 \text{ kg/m}^2$ (2), without evidence of distant metastatic disease, and eligible to undergo concurrent chemotherapy as determined by the treating medical oncologist. Additionally, patients were not allowed to have gastrostomy tube (G-tube) prior to initiation of CRT, nor a history of prior radiotherapy to the head and neck. The CONSORT diagram can be found in [Supplementary Figure 1](#).

Baseline weight was recorded on cycle 1, day 1 of chemotherapy. Once patients lost 5% of their baseline weight, they were recommended exclusive meal replacement with Soylent. For patients who subsequently lost 10% of their baseline weight, they

were recommended G-tube placement. Crossing the 10% weight loss threshold within 3 days of projected treatment completion did not prompt a mandatory G-tube recommendation from the clinical team. Our co-primary endpoints were compliance with Soylent nutritional supplementation during concurrent CRT as well as the G-tube placement rate. Our secondary outcomes were patient-reported QOL scores.

Patient-reported QOL assessments

QOL assessment was performed using 2 previously validated surveys administered at a pre-treatment baseline and at 1, 3, 6, 12, and 18 months of follow-up from completion of treatment. Patients were asked to complete these instruments in paper form in a private setting with the assistance of nursing staff if necessary.

The University of Washington Quality of Life scale (UW-QOL; version 4) is a survey used to evaluate patient-reported QOL outcomes in head and neck cancer (9). The UW-QOL consists of 12 domains pertaining to QOL in the categories of pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, mood, and anxiety. A score of 0 indicates very poor or no functional capacity with regard to that domain whereas a score of 100 indicates no disability in that domain. In the final part of the UW-QOL, patients were asked general questions focused on QOL. This segment was scored with 0 indicating very poor QOL and 100 indicating outstanding QOL, with a range of scores as integer values in between.

The Functional Assessment of Cancer Therapy-Head and Neck scale (FACT-H&N) is also a validated, multidimensional, self-reported QOL instrument specifically designed for use with patients with head and neck cancer (10). It consists of 27 core items that assess patient function in 4 domains (physical, social/family, emotional, and functional well-being), which is supplemented further by 12 site-specific items to assess for head and neck-related symptoms. Each item is rated on a Likert-type scale from 0 to 4, with higher scores representing better QOL, and then combined to produce subscale scores for each domain as well as a global QOL score. The FACT-General (FACT-G) subscore (encompassing physical, social, emotional, and functional well-being subscales) and FACT-H&N subscore (encompassing the head and neck-specific domain alone) were also calculated.

Any patient with a missing survey was excluded in the data set for that particular time point. Only patients with complete baseline pre-treatment questionnaires and at least one complete follow-up questionnaire were considered to have assessable quality of life survey data for the QOL subset analysis.

Statistical analysis

QOL data were presented using descriptive statistics. With normality being assessed via quantile-quantile plot (Q-Q plot) and the Shapiro-Wilk test, paired t-test or the Wilcoxon signed rank test were employed, where appropriate, to compare QOL scores from baseline to follow-up time points. Adjusted p-values were also obtained

via the Benjamini-Hochberg procedure to address the multiple testing problem with a false discovery rate (FDR) threshold of 0.2.

Results

Patient, tumor, and treatment characteristics

60 patients were enrolled. As presented in Table 1, the average age at enrollment was 58 years and the average KPS was 90. 72% of enrolled were male and the majority of patients identified as having non-Hispanic ethnicity (93%). 67% of patients had no history of smoking, whereas 15% had over a 30 pack-year history of smoking. Mean baseline weight was 181 lbs and mean baseline BMI was 27 kg/m².

The most common site treated was the oropharynx (27/60, 45%), followed by the nasopharynx (9/60, 15%). 96% (26/27) of all oropharynx cases were HPV positive, whereas 3/15 (20%) of nasopharyngeal cancers were HPV positive. Overall 8th edition AJCC staging ranged from stage I (17%, 10/60) to stage IV (28%, 17/60).

The majority of patients were prescribed a total dose of 70 Gy (43/60, 72%), though patients were also treated to doses of 66 and 60 Gy. Most patients also received concurrent cisplatin (48/60, 80%), followed by carboplatin in 6/60 patients (10%).

Weight loss outcomes, soylent adherence, and G-tube rates

51/60 (85%) enrolled patients lost 5% of their pre-treatment body weight. Among these 51 patients, all were offered exclusive meal replacement with Soylent, and 48/51 (94%) were successfully transitioned to Soylent. 3/51 (6%) patients either refused or did not tolerate full meal replacement with Soylent due to palatability concerns. Among the 48 patients who lost 5% of their body weight and were transitioned to Soylent, 22/48 patients lost an additional 5% of their pre-treatment body weight, prompting recommendation of G-tube placement. Ultimately, 3/22 (14%) actually underwent G-tube placement, whereas 19/22 (86%) declined G-tube placement (Figure 1). This translated to an overall G-tube rate of 5% (3/60) for the entire cohort.

UW-QOL analysis

For both the UW-QOL and the FACT-H&N surveys, among the 41 patients with evaluable quality of life surveys, the baseline, 1-month, 3-month, 6-month, 12-month, and 18-month post-treatment UW-QOL survey completion rates were 100%, 83%, 73%, 45%, 20%, and 13%, respectively.

At baseline, the mean overall and health-related QOL scores as determined by the UW-QOL were 70.8 and 69.7, respectively. As illustrated in Figure 2, the nadirs for both measures were reached 1 month following completion of CRT, with overall QOL scores of

TABLE 1 Patient, tumor, and treatment characteristics.

Patient Characteristics	Number of Patients (%)
Sex	
Male	43 (72)
Female	17 (28)
Ethnicity	
Non-Hispanic	56 (93)
Hispanic	4 (7)
Smoking History	
None	40 (67)
<10 Pack Years	7 (12)
10-30 Pack Years	4 (7)
>30 Pack Years	9 (15)
Tumor Characteristics	Number of Patients (%)
Primary Tumor Site	
Oropharynx	27 (45)
Nasopharynx	9 (15)
Oral Cavity	7 (11.7)
Other	17 (29)
Cutaneous	6
Larynx	4
Paranasal Sinuses	3
Major Salivary Gland	1
Thyroid	1
Cavernous Sinus	1
Hypopharynx	1
AJCC 8th Edition T-Stage	
Tx	1 (2)
T1	10 (17)
T2	18 (30)
T3	13 (22)
T4	15 (25)
Recurrent	3 (5)
AJCC 8th Edition N-Stage	
Nx	1 (2)
N0	9 (15)
N1	22 (37)
N2	16 (27)
N3	3 (5)
Recurrent	3 (5)

(Continued)

TABLE 1 Continued

Patient Characteristics	Number of Patients (%)
AJCC 8th Edition Overall Stage Grouping	
x	1 (2)
I	10 (17)
II	14 (23)
III	15 (25)
IV	17 (28)
Recurrent	3 (5)
Treatment Characteristics	Number of Patients (%)
Total Radiation Dose	
70 Gy	43 (72)
66 Gy	9 (15)
60 Gy	8 (13)
Systemic Therapy	
Cisplatin	48 (80)
Carboplatin	6 (10)
Carboplatin/Taxol	3 (5)
Cetuximab	3 (5)
Treatment Setting	
Definitive	40 (67)
Adjuvant	20 (33)

61.7 and health-related QOL scores of 51.3. Following the 1-month nadir, patients experienced an improvement in their overall and health-related QOL which numerically exceeded baseline by the 6-month time point, with a slight decline in scores at the 12-month mark, followed by a subsequent increase in scores to 80 and 77.1 by 18 months post completion of therapy. Overall QOL scores were not significantly different between baseline and any time point (Table 2).

Figure 3 illustrates QOL scores segregated by domains relevant to the treatment of head and neck cancer. A similar trend was observed across most domains with a nadir at 1 month, which was especially prominent for taste. Scores eventually rebounded to exceed baseline by 18 months. Comparing individual domain scores from baseline to 18 months, significant differences were found in only two domains. Saliva scores decreased significantly from 91 to 73 (adjusted p-value = 0.02), whereas anxiety scores increased significantly from 51 to 81 (adjusted p-value = 0.11). Adjusted p-values for comparisons between all-time points and baseline are presented in Table 2.

FACT H&N QOL analysis

The FACT-H&N QOL survey results are outlined in Table 3. At baseline, the mean total score, FACT-G subscore, and H&N

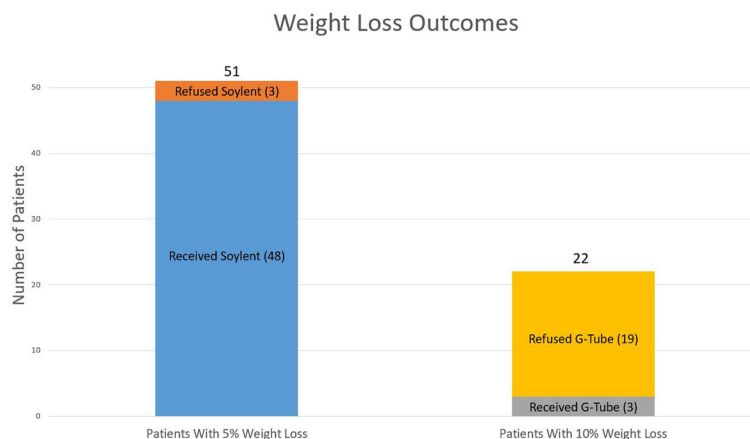


FIGURE 1

Weight loss outcomes. Weight loss outcomes from the 51 patients who lost 5% of their baseline weight as well as the 22 patients who lost 10% of their baseline weight.

subscore was 116.8, 85.2, and 31.6, respectively. At 1 month following completion of CRT, the corresponding values were 98.0, 78.3, and 19.7, respectively, each of which was significantly depressed from baseline and represented the nadirs during the post-treatment period (adjusted $p < 0.05$ for all). However, at 3 months following treatment, only the total score and H&N subscore remained significantly depressed. By 6 months, all scores were not significantly different from baseline, and this remained the case until 18 months of follow-up (adjusted $p > 0.02$ for all). The p -values for all FACT QOL comparisons can be found in Table 3.

Discussion

In patients undergoing conventional, non-deescalated concurrent CRT for head and neck cancer, we report a high adherence rate of 94% with exclusive Soylient meal replacement

when patients lose 5% of their pre-treatment body weight. We also observed a 5% incidence rate of G-tube placement for the total cohort of enrolled patients, which compares favorably to our historical institutional G-tube placement rate of 30% and the G-tube rate of 61% reported on contemporary NRG studies (7). We also report a return to baseline patient-reported QOL according to two survey instruments by 6 months after a nadir in quality of life at 1 month post-treatment.

While several prospective studies have evaluated the value of oral supplementation during radiation alone for head and neck cancer, few studies have evaluated this in the setting of concurrent CRT, where side effects are more severe (11). These studies were also largely conducted in an era prior to modern intensity modulated radiotherapy (IMRT) for head and neck cancer, which has improved short-term and long-term toxicities like xerostomia and dysphagia, which can affect nutritional intake (12, 13). Our results suggest that even in the IMRT era, aggressive nutritional

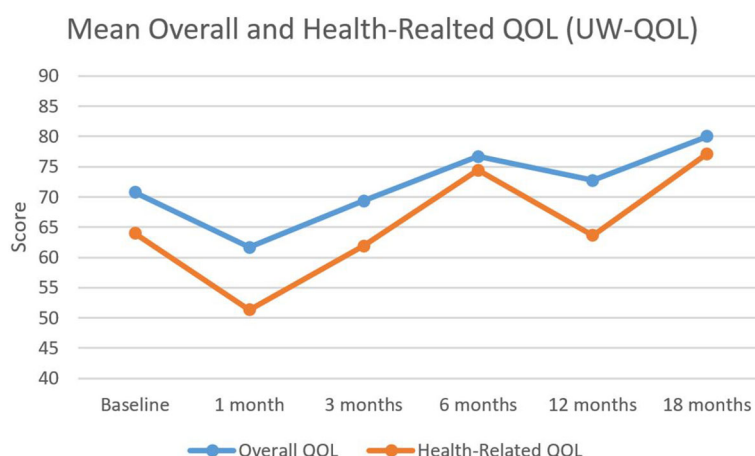


FIGURE 2

Mean overall and health-related QOL outcomes. Mean overall and health-related quality of life as assessed by the University of Washington Quality of Life (UW-QOL) survey instrument for the 41 patients with assessable questionnaires.

monitoring and oral liquid meal replacement contribute to the expeditious return of QOL and yield low G-tube rates.

The favorable oncologic outcomes for patients with head and neck cancers, especially in the HPV+ subset (14), has consequently refocused much needed attention onto strategies that improve QOL in this cancer population. In the modern treatment era, our study demonstrates favorable QOL outcomes are achievable following exclusive Soylent meal replacement and prompts reflection on the role of simple, creative, and low-tech avenues for improving QOL in head and neck cancer patients.

An interesting finding is the decrement in both overall and health-related QOL at 12 months as assessed by the UW instrument, in spite of prior gains in these metrics at the 3- and 6-month time points. This appeared to be driven by decrements in

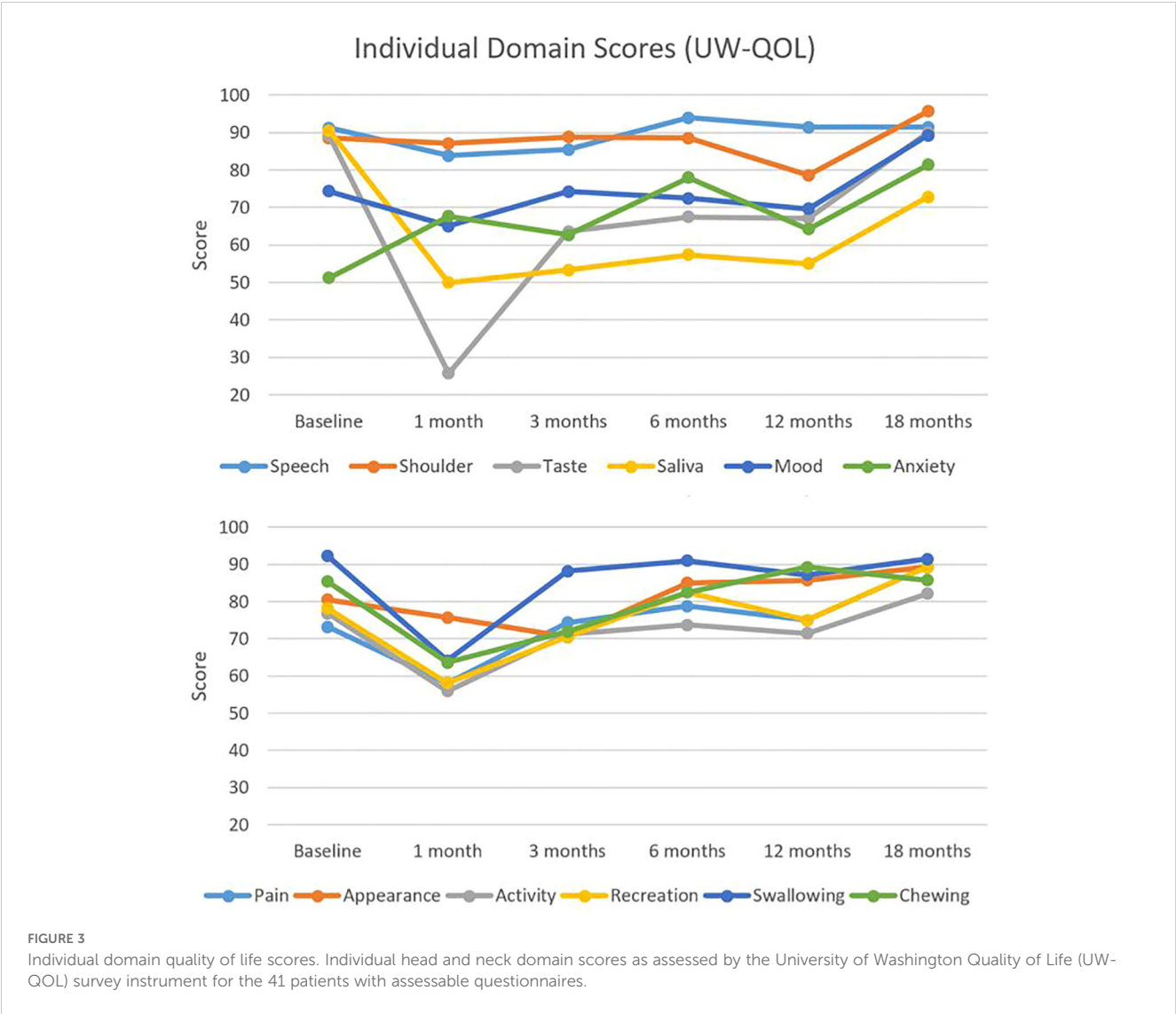
scores related to anxiety, shoulder motion, and recreation, which might be explained by anxiety surrounding surveillance imaging at the 1-year time point or late-developing fibrotic sequelae of CRT.

Though differences in patient populations and treatment techniques mean that direct comparisons with other studies evaluating separate research questions should be undertaken with caution, it is nonetheless interesting to appreciate the similarities in QOL profiles across similar time points in patients who were also enrolled on a phase II study of de-escalated CRT at our institution between October 2012 and March 2015. In a companion QOL analysis from patients enrolled on that trial, Hegde et al. also demonstrated return to baseline FACT-G subscores at 3 months, and normalization of FACT-HN subscores and mean total scores by 6 months. These findings represented an improvement in QOL

TABLE 2 UW-QOL scores.

	Baseline	1 month	3 months	6 months	12 months	18 months
	(stdev)	(stdev)	(stdev)	(stdev)	(stdev)	(stdev)
Overall Score	70.8 (20.4)	61.7 (21.3)	69.4 (21.5)	76.7 (25.0)	72.7 (20.5)	80.0 (23.1)
Adjusted p-value	–	0.45	0.54	0.45	0.8	0.71
Pain Subscore	73.2 (25.9)	58.1 (27.3)	74.4 (26.2)	78.8 (21.9)	75.0 (24.0)	89.3 (19.7)
Adjusted p-value	–	0.35	1.00	0.82	0.82	1.00
Appearance Subscore	80.5 (20.5)	75.7 (15.7)	70.5 (18.2)	85.0 (18.9)	85.7 (12.8)	89.3 (13.4)
Adjusted p-value	–	0.61	p=0.03	0.27	1.00	0.75
Activity Subscore	76.8 (21.9)	55.9 (20.5)	71.2 (19.9)	73.8 (22.2)	71.4 (30.8)	82.1 (23.8)
Adjusted p-value	–	p<0.01	0.30	1.00	0.33	1.00
Recreation Subscore	78.1 (20.6)	58.1 (19.2)	70.5 (18.2)	82.5 (18.3)	75.0 (31.0)	89.3 (13.4)
Adjusted p-value	–	p<0.001	p=0.02	0.38	0.38	1.00
Swallowing Subscore	92.3 (15.8)	64.1 (26.8)	88.2 (14.9)	91.0 (14.1)	87.1 (15.4)	91.4 (14.6)
Adjusted p-value	–	p<0.001	p=0.06	0.48	0.22	0.43
Chewing Subscore	85.4 (23.05)	63.6 (33.7)	71.9 (28.2)	82.5 (24.5)	89.3 (21.3)	85.7 (24.4)
Adjusted p-value	–	p<0.01	p=0.06	0.77	0.77	0.77
Speech Subscore	91.2 (13.8)	83.8 (21.0)	85.5 (15.2)	94 (12.3)	91.4 (14.1)	91.4 (14.6)
Adjusted p-value	–	p=0.10	p=0.10	1.00	1.00	1.00
Shoulder Subscore	88.5 (21.3)	87.1 (30.1)	88.8 (26.4)	88.5 (27.2)	67.1 (27.6)	95.7 (11.3)
Adjusted p-value	–	1.00	1.00	1.00	p=0.06	1.00
Saliva Subscore	90.5 (18.5)	50 (28.2)	53.3 (29.3)	57.4 (32.6)	55.0 (29.8)	72.9 (23.6)
Adjusted p-value	–	p<0.001	p<0.001	p<0.01	p<0.01	p=0.02
Taste Subscore	89.3 (21.4)	25.8 (26.9)	63.6 (26.1)	67.5 (25.5)	67.1 (27.6)	90.0 (26.5)
Adjusted p-value	–	p<0.001	p<0.001	p<0.01	p<0.01	1.00
Mood Subscore	74.4 (21.0)	65.1 (25.3)	74.2 (22.1)	72.5 (21.3)	69.6 (28.0)	89.3 (19.7)
Adjusted p-value	–	0.21	0.94	1.00	0.47	1.00
Anxiety Subscore	51.2 (29.7)	67.7 (24.5)	62.7 (30.0)	78.0 (26.5)	64.3 (34.4)	81.4 (26.7)
Adjusted p-value	–	p<0.01	p=0.06	p<0.01	0.28	0.11
Percent Change in Overall Score	–	-12.85%	+18.36%	+20.62%	+24.15%	+32.06%

Table presents adjusted p-values. Bolded values are significant (p-value threshold of 0.2).



outcomes with de-escalation compared to historical controls in their study and highlighted the promise of de-escalation efforts for improving QOL. That we observed similar time to baseline QOL recovery across similar metrics using identical survey instruments at the same institution suggests that aggressive nutritional replacement may plays a similarly powerful role in abrogating CRT toxicity in the treatment of head and neck cancers. In contrast however to the companion QOL study, patients in the present study did not experience a significant increase in FACT scores above baseline by 18 months, which is contextualized by the

TABLE 3 FACT-QOL scores.

	Baseline	1 month	3 months	6 months	12 months	18 months
	(stdev)	(stdev)	(stdev)	(stdev)	(stdev)	(stdev)
Mean FACT-G Subscore (SD)	85.2 (11.5)	78.3 (14.3)	83.8 (16.3)	85.4 (12.9)	87.9 (12.4)	93.5 (10.3)
Adjusted p-value	–	p<0.02	0.87	0.68	0.88	0.48
Mean H&N Subscore (SD)	31.6 (6.8)	19.7 (7.3)	26.0 (6.6)	28.8 (6.0)	29.7 (4.0)	26.7 (6.9)
Adjusted p-value	–	p<0.001	p<0.001	0.57	0.61	0.57
Mean Total Score (SD)	116.8 (16.0)	98.0 (19.9)	109.8 (21.4)	114.3 (17.5)	117.6 (15.4)	120.3 (16.1)
Adjusted p-value	–	p<0.001	p<0.02	1.00	1.00	1.00
Percent Change in Total Score	–	-16.06%	-5.98%	-2.11%	+0.69%	+02.96%

Table presents adjusted p-values. Bolded values are significant (p-value threshold of 0.2).

fact that these patients were receiving standard non-de-escalated CRT. It may also be worth noting that the G-tube rate on this study compares favorably with our institution's historical G-tube rate of 30%.

An important limitation of this study is that we are not able to disentangle potential synergistic QOL effects between aggressive nutritional counseling, dietary monitoring, and consumption of Soylent as a meal replacement itself. However, Soylent as a nutritional agent is the subject of ongoing clinical investigation, including its impact on human microbiome composition (NCT 03203044). Thus, future studies may be able to better elucidate the relative benefits and tradeoffs of Soylent specifically as a nutritional agent in clinical settings.

It is also true that our favorable quality of life outcomes and low G-tube rates could be explained by a patient population with generally favorable performance status attributes or by improvements in supportive care, systemic therapies, and radiation therapy. However, even in modern series, G-tube rates can be quite high in patients receiving full dose standard of care CRT. For example, despite improvements in the delivery of local and systemic therapies, a recent multi-institutional study of patients with oropharyngeal cancer revealed that 82% of patients receiving concurrent CRT with IMRT required G-tube insertion, albeit approximately half in the therapeutic, rather than prophylactic, setting (15). However, we recognize that variation in institutional practice patterns is also likely to play a significant role in the rates of G-tube insertion. Specifically, patients undergoing CRT who engage in regular swallowing exercises alongside rigorous oral intake strategies have been shown to experience less severe treatment-related dysphagia (16), and thus rigorous referral of all patients undergoing head and neck CRT to speech language pathologists prior to treatment initiation (as is customary at our institution) may also simultaneously be driving the low G-tube rates reported herein.

Of course, treatment de-escalation is another approach for improving QOL that has become of significant interest in recent years, particularly for the HPV positive subset of head and neck cancer patients. Rates of feeding tube insertion from landmark studies (17) of de-escalation therapy do appear to be on-par with our rates, with pre-and post-treatment rates of 1.3% 2.8% in the 60 Gy plus cisplatin arm of NRG HN002 and rates of 0% and 3.8% in the 60 Gy alone arm. Moreover, in a recently published quality of life analysis from the single institution phase II de-escalation study MC1273, FACT-HN scores at 12 months were remarkably high at 117.2 pre-RT, which increased to 127.2 at 12 months of follow-up (18). While this study focused exclusively on patients requiring adjuvant therapy and thus only a subset of patients received CRT as part of trimodality therapy, this nonetheless suggests that deploying treatment de-escalation strategies may result in patient-reported QOL gains that surpass nutritional interventions alone, but are likely to be complementary to QOL gains achieved from nutritional intervention. However, it is important to note that at the time of this writing, the safety of de-escalation has yet to be proven in the randomized phase 3 setting, and thus standard of care for all head and neck cancer patients remains full dose CRT. Aggressive nutritional management with nutritional adjuncts such as Soylent

may serve as an effective bridge to maintaining high quality of life even in the face of full dose CRT while the results of practice-changing de-escalation studies are eagerly awaited.

Maintenance of QOL during treatment for head and neck cancer results from a complex interplay of patient, tumor, treatment, and provider-related factors. However, predictors of poor QOL and thus appropriate mitigating strategies are sometimes unexpected, as illustrated by a recent narrative literature review suggesting that patients undergoing curative intent protocols who were more advanced in age tended to demonstrate increased resilience and QOL outcomes (19) when compared to their younger counterparts. Thus, if our prevailing aim is to reduce toxicity from curative head and neck CRT courses, our efforts should not simply focus on the “high-tech” intuitive strategies such as reducing radiation or cytotoxic chemotherapy dosing, but instead should leverage the full spectrum of modern multidisciplinary cancer care (including “low-tech” solutions such as aggressive nutritional monitoring and supplementation) in order to make meaningful inroads in the improvement of QOL outcomes for this critical population of cancer patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by University of California Los Angeles. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LV: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. FC: Writing – review & editing, Formal analysis, Methodology. XW: Writing – review & editing, Formal analysis, Methodology. AE: Writing – review & editing, Investigation, Project administration, Resources. JH: Writing – review & editing, Data curation, Project administration. EK: Writing – review & editing, Investigation, Project administration, Resources. NE: Writing – review & editing, Data curation. AR: Writing – review & editing, Investigation. DW: Writing – review & editing, Conceptualization, Investigation. MS: Writing – review & editing, Project administration, Resources, Supervision. AK: Writing – review & editing, Investigation. RC: Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources. JVH: Writing – review & editing, Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources.

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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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Intraoperative circulation predict prolonged length of stay after head and neck free flap reconstruction: a retrospective study based on machine learning

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Background: Head and neck free flap reconstruction presents challenges in managing intraoperative circulation, potentially leading to prolonged length of stay (PLOS). Limited research exists on the associations between intraoperative circulation and PLOS given the difficulty of manual quantification of intraoperative circulation time-series data. Therefore, this study aimed to quantify intraoperative circulation data and investigate its association with PLOS after free flap reconstruction utilizing machine learning algorithms.

Methods: 804 patients who underwent head and neck free flap reconstruction between September 2019 and February 2021 were included. Machine learning tools (Fourier transform, et al.) were utilized to extract features to quantify intraoperative circulation data. To compare the accuracy of quantified intraoperative circulation and manual intraoperative circulation assessments in the PLOS prediction, predictive models based on these 2 assessment methods were developed and validated.

Results: Intraoperative circulation was quantified and a total of 114 features were extracted from intraoperative circulation data. Quantified intraoperative circulation models with a real-time predictive manner were constructed. A higher area under the receiver operating characteristic curve (AUROC) was observed in quantified intraoperative circulation data models (0.801 [95% CI, 0.733–0.869]) compared to manual intraoperative circulation assessment models (0.719 [95% CI, 0.641–0.797]) in PLOS prediction.

Conclusion: Machine learning algorithms facilitated quantification of intraoperative circulation data. The developed real-time quantified intraoperative circulation prediction models based on this quantification offer a potential strategy to optimize intraoperative circulation management and mitigate PLOS following head and neck free flap reconstruction.

KEYWORDS

intraoperative circulation, time series data, machine learning, free flap reconstruction, prolonged length of stay

1 Introduction

In the realm of microsurgery, free flap transplantation has emerged as a standard technique for reconstructing head and neck defects resulting from maxillofacial tumors resection and osteonecrosis. This procedure presents certain characteristics that pose challenges in managing intraoperative circulation and can potentially hinder postoperative rehabilitation. These include prolonged duration, extensive wounds, and intricate and delicate procedures (1).

The duration of hospitalization after surgery, referred to as length of stay (LOS), serves as a crucial metric evaluating the quality encompassing free flap reconstruction and postoperative rehabilitation. Prolonged length of stay (PLOS) strongly links to increased healthcare expenses and elevated postoperative complications, impacting patients' quality of life (2). However, patients' average LOS might surpass 10 days (3). Hence, optimizing rehabilitation methods and reducing LOS following free flap reconstruction becomes crucial. The influence of perioperative events on patients' LOS is apparent in addition to surgical procedures (4), and efforts made in perioperative management have a crucial role to play in preventing PLOS (5–7).

Intraoperative circulation management, as an important part of perioperative management of free flap reconstruction, clearly deserves attention. Previous works have reported that in non-cardiac surgery, aberrant intraoperative circulatory state, including intraoperative hypotension (8–11), rapid heart rate (12, 13), abnormally elevated blood pressure (14) affect patients' prognosis (myocardial injury, renal damage, 30-day mortality, etc.) and increase incidence of PLOS (15). To better appraise intraoperative circulation, variability of blood pressure, time-weighted hypotension (16, 17) and hypertension (17) were developed in addition to the above. However, the influence of intraoperative circulation during free flap reconstruction on the occurrence of PLOS has been rarely documented, warranting further exploration.

In addition, intraoperative circulation is made up of time series data. The traditional assessment variables mentioned earlier have limitations in effectively reflecting the variability of intraoperative circulation during surgery and the complex interconnections between these variables. Xue et al. reported that the association

between intraoperative circulation and postoperative adverse events in non-cardiac surgery can be evaluated more accurately using the time-series data assessment metrics (18). Furthermore, the emergence of machine learning algorithms in the medical field has provided novel solutions for evaluating and modifying the intraoperative circulation data. Hatib F et al. developed a machine-learning-based predictive model for early warning of intraoperative hypotension based on arterial pressure waveforms (19), which was replicated and found to be effective by Wijnberge. M. et al. (20). Furthermore, using machine learning algorithms like Fourier transformation and Ricker wavelet analysis, extracting features for time series data processing was no longer a challenging task (21–23).

Therefore, employing machine learning algorithms, the purpose of this retrospective study was to assess and evaluate the predictive impact of quantified intraoperative circulation data on head and neck surgery with free flap reconstruction. It was hypothesized that the use of machine learning algorithms would provide a more thorough view of the relationship between intraoperative circulation data and PLOS after free flap reconstruction. The first aim of this study was to extract intraoperative circulation data eigenvalues using machine learning algorithms for their quantification. The second aim of this study was to investigate the potential superiority of quantified intraoperative circulation data over manual assessment metrics in predicting PLOS.

2 Materials and methods

2.1 Ethics

Ethical approval was obtained from the Institutional Review Board (IRB) of Sun Yat-sen Memorial Hospital, Sun Yat-sen University.

2.2 Study design

The medical records of patients who underwent head and neck surgery with free flap reconstruction at Sun Yat-sen Memorial

Hospital between September 2019 and February 2021 were collected and randomly assigned into primary and validation cohorts in a ratio of 8:2 in the present retrospective study. Eligibility criteria required individuals to have received head and neck surgery with free flap reconstruction during the designated period. And exclusion criteria were as follows: missing values of demographic characteristics, perioperative laboratory examination data, surgical or fluid variables, missing intraoperative blood pressure, heart rate or pulse values for > 10 min, and patients younger than 9 years old.

Before anesthesia induction, arterial blood pressure was measured invasively with an arterial catheter placed into the radial artery and was recorded together with heart rate and pulse at 5-minute intervals. Arterial blood pressures, heart rates, and pulse values were linearly interpolated between readings (11). In the present study, mean arterial pressure (MAP) was calculated from systolic and diastolic blood pressure. The threshold of hypertension and hypotension was defined as 30% above and below the baseline MAP (MAP before induction), respectively. Time-weighted (TW) hypertension during surgery was calculated as the product of the depth of hypertension above the threshold of hypertension (mmHg) multiplied by the time above the threshold of hypertension (min). Similarly, TW hypotension during surgery was calculated as the depth of hypotension below the threshold of hypotension (mmHg) × the time below the threshold of hypotension (min). Intraoperative average real variability (ARV) and squared version of the generalized ARV (ARVs) of MAP were calculated by the following formula (16):

$$ARV = \frac{1}{T} \sum_{k=1}^{N-1} t |MAP_{k+1} - MAP_k|$$

$$ARVs = \frac{1}{T} \sum_{k=1}^{N-1} \frac{|MAP_{k+1} - MAP_k|^2}{t_{k+1} - t_k}$$

T was the total time between the first and last MAP reading, N is the number of MAP readings and t is the time interval between each set of readings, MAP_k and MAP_{k+1} .

Meanwhile, to quantify intraoperative circulation time series data, machine learning-based technologies (including Fourier transform, Ricker wavelet, Lempel-Ziv compression, approximation entropy, permutation entropy, linear regression following blocks aggregation, and percentage of duplicate and non-duplicate values) were implemented with a dual test false discovery rate (FDR) of 0.01 in the current work to obtain the eigenvalues from patients' intraoperative circulation time series data.

In the current study, each patient received a standardized anesthetic approach that included sevoflurane and opioids (sufentanil and remifentanil) for maintenance, as well as vasopressors if the patient experienced prolonged hypotension.

2.3 Data collection

From patients' medical records, demographic information such as sex, age, body mass index (BMI), the reason for the flap (benign or malignant tumor, osteoradionecrosis), flap types (fibular flap, anterolateral thigh flap, posterior tibial artery flap, radial forearm

flap, or others), American Society of Anesthesiologists (ASA) status, smoking history, radiotherapy history, and comorbidities (hypertension, diabetes, stroke, coronary heart disease, and others) were collected. The BMI was calculated using the height and weight of the patients.

Preoperative lab examination data, including hemoglobin (Hb), albumin, serum C-reactive protein (CRP), and differential blood cell counts, were collected seven days before surgery. Data from postoperative laboratory examinations, including Hb, albumin, and differential blood cell counts, were gathered within one day after surgery. Based on the blood cell counts, the perioperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were computed.

Surgical variables included intraoperative blood loss, duration of surgery, vasopressor administration, intraoperative blood transfusion, urine output and postoperative ICU admission. The conscious decision to use vasopressors (i.e. norepinephrine, dopamine or ephedrine) on a case-by-case basis was made by the anesthesia crew. A blood transfusion was required when the hemoglobin (Hb) level was lower than 70 g/L or the hematocrit (Hct) was lower than 25% in patients with uncompromised function (cardiac or pulmonary). A blood transfusion was indicated when Hct was less than 25% for patients younger than 60 years and less than 30% for patients older than 60 years in hemodynamically impaired patients.

Fluid variables included the volume and rate of both intraoperative infusion and 24-hour infusion (crystalloid, colloid and total). The infusion rate was standardized to the patient's body weight (mL/[kg×hr]). Intraoperative fluid infusions were administered at the discretion of the anesthesiologists based on intra-arterial blood pressure monitoring (avoided the occurrence of intraoperative hypertension or hypotension), stroke volume variation (maintained between 10-15) and the patient's urine output (maintained no lower than 1 mL/[kg×hr]). The surgical crew was responsible for titrating the rate of postoperative fluid infusions considering the patient's heart rate, blood pressure, and urine output.

2.4 Outcome

Length of stay (LOS) stands for the total number of days between surgery and discharge, and PLOS stands for any length of stay above the median of LOS.

2.5 Statistical analysis

Continuous variables were presented as mean (SD) or median (quartiles) based on their normalcy. To summarize categorical variables, frequencies (percentages, %) were employed. Continuous variables were analyzed using the t-test or the Mann-Whitney U test, depending on their normality. Categorical variables were analyzed using the chi-square or Fisher exact test, depending on their frequency of occurrence.

Between the primary and validation cohorts, the univariable association of baseline demographic data, perioperative laboratory

examination parameters, surgical factors, fluid variables and LOS was examined. The median LOS was used to divide patients into PLOS and Non-PLOS groups. The primary cohort's PLOS and Non-PLOS groups were then compared using univariate and multivariate logistic regression analysis to determine risk factors for PLOS. Collinearity diagnostics were performed to determine the features for multivariable comparison.

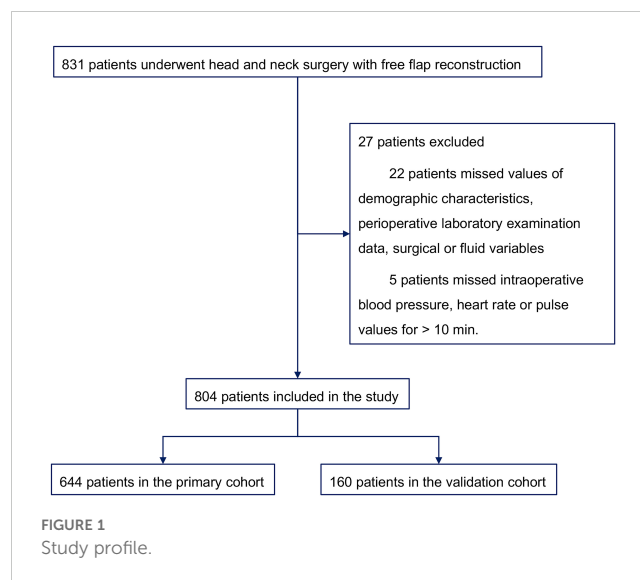
Features derived from two intraoperative circulation data evaluation methods were estimated in the present study. One was the features of manual intraoperative circulation data evaluations which included the intraoperative TW hypertension, TW hypotension, ARV and ARVs. Another was the features extracted from intraoperative circulation time series data through machine learning-based tools (including Fourier transform, Ricker wavelet, etc.). Occasional missing points in intraoperative circulation data were filled by the average of adjacent data points. The min-max normalization was utilized for data pre-processing after intraoperative circulation data features extraction. To determine and compare the predictive value of these two intraoperative circulation data evaluation methods, random forest and xgboost algorithms were utilized incorporating features from different intraoperative circulation evaluation methods and other clinical features in the primary cohort to evaluate feature relevance and develop binary classification predictive models for PLOS after free flap reconstruction. The Shapley additive explanations (SHAP) algorithm was applied to our prediction models to evaluate the importance of features. The receiver operating characteristic curve (ROC) and confusion matrix was drawn, and the area under the receiver operating characteristic curve (AUROC) and overall accuracy (OA) was calculated to evaluate the accuracy of these predictive models. The eigenvalues of intraoperative circulation data extracted through machine learning algorithms dynamically evolved as the intraoperative circulation data accumulated. Correspondingly, the risk probabilities derived from predictive models incorporating these features varied accordingly. Therefore, these risk probabilities were referred to as prediction scores, which were systematically calculated and analyzed in this study.

Univariable and multivariable analysis was performed with IBM SPSS software (version 25.0; SPSS Inc, Chicago, IL). Machine learning algorithms (Fourier transform, ricker wavelet, Lempel-Ziv compression algorithm, random forest, xgboost, etc.) were performed with Python (version 3.8.5). Differences with a $p < 0.05$ significance level were deemed statistically significant.

3 Results

3.1 Patients and clinical characteristics

A total of 831 individuals who underwent head and neck surgery with free flap reconstruction were initially included. 22 patients were excluded for missing values on demographic characteristics, perioperative laboratory data, surgical or fluid variables, 5 patients were removed due to missing intraoperative blood pressure, heart rate or pulse values for > 10 min, resulting in a final enrollment of 804. Among them, 644 participants formed the



primary cohort and 160 the validation cohort (Figure 1). Median LOS was 10 days, with 25% and 75% quartiles of 8 and 12 days, respectively. Those with LOS exceeding 10 days were classified as PLOS, while LOS no higher than 10 days were Non-PLOS cases. Table 1 summarizes of the demographic characteristics of patients along with perioperative laboratory examination data, surgical and fluid factors for both the primary and validation cohorts.

3.2 Univariate and multivariate comparisons between the PLOS and Non-PLOS groups in the primary cohort

Within the primary cohort, uncovering differences between the PLOS and Non-PLOS groups, variables including Age, smoking status, history of hypertension, total comorbidities, preoperative albumin and NLR levels, postoperative hemoglobin and albumin levels, blood loss, duration of surgery, intraoperative RBC and FFP transfusion, fluid infusion rate over 24 hr, postoperative ICU admission, and reoperation emerged as significantly distinct following univariate comparisons (Table 2). Furthermore, smoking status (odds ratio [OR] = 0.566; 95% CI, 0.373–0.861; $p = 0.008$), intraoperative RBC transfusion (OR = 1.141; 95% CI, 1.005–1.295; $p = 0.042$) and postoperative reoperation (OR = 0.110; 95% CI, 0.038–0.323; $p < 0.001$) were identified as independent risk factors for PLOS in patients who underwent head and neck surgery with free flap reconstruction (Table 2).

3.3 Quantification of intraoperative circulation data

In order to quantify the intraoperative circulation (systolic, diastolic blood pressure, pulse and heart rate) data, a total of 114 features was extracted using machine learning-based technologies (Fourier transform, Ricker wavelet, Lempel-Ziv compression algorithm, approximation entropy, permutation entropy, linear

TABLE 1 Univariate Analysis between the Primary and Validation cohorts.

	Primary Cohort (n=644)	Validation Cohort (n=160)	Univariate (<i>P</i> value)
Sex (male), No. (%)	419 (65.1)	98 (61.3)	0.368
Age, mean (SD), yr	55.83 (13.92)	54.60 (15.20)	0.327
Reason for Flap, No. (%)			0.277
Tumor	593 (92.1)	151 (94.4)	
Osteoradionecrosis	50 (7.8)	8 (5.0)	
Others	1 (0.2)	1 (0.6)	
BMI, mean (SD), kg/m ²	22.50 (3.61)	22.31 (3.41)	0.549
Flap Types, No. (%)			0.418
Fibular Flap	199 (30.9)	42 (26.3)	
Anterolateral Thigh Flap	306 (47.5)	74 (46.3)	
Posterior Tibial Artery Flap	95 (14.8)	33 (20.6)	
Radial Forearm Flap	23 (3.6)	5 (3.1)	
Other	21 (3.3)	6 (3.8)	
ASA Status, No. (%)			0.219
I or II	342 (53.1)	86 (53.8)	
III	290 (45.0)	74 (46.3)	
IV	12 (1.9)	0 (0.0)	
Smoking Status, No. (%)	205 (31.8)	44 (27.5)	0.289
Comorbidities, No. (%)			
Hypertension	144 (22.4)	26 (16.3)	0.090
Diabetes Mellitus	60 (9.3)	12 (7.5)	0.471
Stroke	16 (2.5)	5 (3.1)	0.587
Coronary Heart Disease	18 (2.8)	6 (3.8)	0.525
Other	22 (3.4)	7 (4.4)	0.560
Total	195 (30.3)	41 (25.6)	0.247
Radiotherapy History, No. (%)	93 (14.4)	17 (10.6)	0.209
Preoperative			
Hemoglobin, mean (SD), g/L	132.39 (18.22)	133.06 (17.95)	0.678
Albumin, mean (SD), g/L	37.72 (4.70)	37.81 (4.46)	0.812
NLR, median (quartiles)	2.34 (1.67, 3.28)	2.47 (1.59, 3.49)	#0.620
PLR, median (quartiles)	146.01 (114.02, 198.53)	147.21 (116.54, 198.13)	#0.889

(Continued)

TABLE 1 Continued

	Primary Cohort (n=644)	Validation Cohort (n=160)	Univariate (<i>P</i> value)
Postoperative			
Hemoglobin, median (quartiles), g/L	111.00 (98.00, 123.00)	110.00 (101.00, 122.00)	#0.699
Albumin, median (quartiles), g/L	30.40 (27.20, 33.30)	30.50 (27.60, 34.50)	#0.214
NLR, median (quartiles)	15.33 (10.01, 22.70)	16.28 (11.22, 26.44)	#0.103
PLR, median (quartiles)	251.64 (173.24, 366.69)	289.56 (192.53, 418.47)	#0.072
Blood Loss, median (quartiles), ml	300.00 (200.00, 400.00)	300.00 (200.00, 400.00)	#0.406
Duration of Surgery, median (quartiles), min	375.00 (290.00, 455.00)	365.00 (290.00, 465.00)	#0.670
Intraoperative Fluid Infusion, median (quartiles), ml	3000 (2500, 3500)	3000 (2500, 3500)	#0.953
Intraoperative Fluid Infusion Rate, median (quartiles), ml/(kg×h)	8.13 (6.47, 9.74)	8.42 (6.67, 10.25)	#0.104
Intraoperative RBC Transfusion, median (quartiles), u	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	#0.359
Intraoperative FFP Transfusion, median (quartiles), ml	0.0 (0.0, 200.0)	0.0 (0.0, 100.0)	#0.237
Intraoperative Urine Output, median (quartiles), ml	700.0 (450.0, 1000.0)	775.0 (500.0, 1000.0)	#0.229
Fluid Infusion over 24 hr, median (quartiles), ml	4200 (3500, 4900)	4300 (3650, 5000)	#0.431
Fluid Infusion Rate over 24 hr, median (quartiles), ml/(kg×h)	2.91 (2.39, 3.56)	3.08 (2.50, 3.70)	#0.119
Postoperative ICU Admission, No. (%)	42 (6.5)	10 (6.3)	0.900
Reoperation, No. (%)	39 (6.1)	7 (4.4)	0.413
Vasopressor Administration, No. (%)	146 (22.7)	31 (19.4)	0.368

BMI, Body Mass Index; ASA, American Society of Anesthesiologists; RBC, red blood cell; FFP, free-frozen plasma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte- to-monocyte ratio.
The *P* value is derived from the univariable association analyses between the primary and validation cohorts.
indicates that the Mann-Whitney U test was utilized.

regression following blocks aggregation, and percentage of duplicate and non-duplicate values) with 0.01 dual test false discover rate (Supplementary Table S1).

3.4 Quantified intraoperative circulation data predicted the occurrence of PLOS

To evaluate predictive capabilities of quantified intraoperative circulation data, random forest and xgboost methods were utilized for predictive model creation due to their strengths in handling extensive feature amounts. Additionally, a comparison was made between features extracted from intraoperative circulation time series data using machine learning-based algorithms and features derived from

manual intraoperative circulation evaluations. Both sets of features were utilized in building predictive models with the same algorithms, along with other relevant perioperative clinical factors.

The predictive models were successfully developed, and the significance of the incorporated features was measured using SHAP values (Figure 2). Besides, the trend of the SHAP value of the top 10 important features in each model were shown in Supplementary Figure S1. In both random forest (Model 1) and xgboost (Model 2) models, specific features derived from quantified intraoperative circulation data were found to be associated with the occurrence of PLOS following free flap reconstruction (Figures 2A, B; Supplementary Figures S1A, B). On the other hand, features obtained from manual intraoperative circulation assessments such as intraoperative TW hypotension, AVR and AVRs emerged as predictive factors for PLOS (Figures 2C,

TABLE 2 Univariate and Multivariate Comparisons between the PLOS and Non-PLOS Groups in the Primary Cohort.

	PLOS (n=340)	Non-PLOS (n=304)	Univariate (<i>P</i> value)	Multivariate [<i>P</i> value (OR; 95% CI)]
Sex (male), No. (%)	230 (67.6)	189 (62.2)	0.146	0.950 (1.013; 0.667 to 1.539)
Age, mean (SD), yr	56.93 (14.47)	54.60 (13.19)	0.034	0.656 (1.003; 0.988 to 1.019)
Reason for Flap, No. (%)			0.563	
Tumor	313 (92.1)	280 (92.1)		
Osteoradionecrosis	27 (7.9)	23 (7.6)		
Others	0 (0.0)	1 (0.3)		
BMI, mean (SD), kg/m ²	22.28 (3.70)	22.74 (3.49)	0.106	0.962 (0.998; 0.937 to 1.064)
Flap Types, No. (%)			0.052	0.377
Fibular Flap	102 (30.0)	97 (31.9)		0.939 (1.039; 0.388 to 2.784)
Anterolateral Thigh Flap	175 (51.5)	131 (43.1)		0.477 (1.424; 0.538 to 3.772)
Posterior Tibial Artery Flap	38 (11.2)	57 (18.8)		0.994 (0.996; 0.345 to 2.874)
Radial Forearm Flap	14 (4.1)	9 (3.0)		0.341 (1.877; 0.514 to 6.856)
Other	11 (3.2)	10 (3.3)		
ASA Status, No. (%)			0.414	0.696
I or II	174 (51.2)	168 (55.3)		0.440 (1.769; 0.415 to 7.530)
III	158 (46.5)	132 (43.4)		0.517 (1.589; 0.391 to 6.464)
IV	8 (2.4)	4 (1.3)		
Smoking Status, No. (%)	127 (37.4)	78 (25.7)	0.001	0.008 (0.566; 0.373 to 0.861)
Comorbidities, No. (%)				
Hypertension	89 (26.2)	55 (18.1)	0.014	0.269 (0.671; 0.331 to 1.362)
Diabetes Mellitus	38 (11.2)	22 (7.2)	0.086	
Stroke	12 (3.5)	4 (1.3)	0.080	
Coronary Heart Disease	12 (3.5)	6 (2.0)	0.232	
Other	11 (3.2)	11 (3.6)	0.789	
Total	117 (34.4)	78 (25.7)	0.016	0.847 (0.937; 0.486 to 1.809)
Radiotherapy History, No. (%)	53 (15.6)	40 (13.2)	0.381	0.891 (0.964; 0.569 to 1.633)

(Continued)

TABLE 2 Continued

	PLOS (n=340)	Non-PLOS (n=304)	Univariate (P value)	Multivariate [P value (OR; 95% CI)]
Preoperative				
Hemoglobin, mean (SD), g/L	131.83 (19.15)	133.02 (17.12)	0.409	
Albumin, mean (SD), g/L	37.13 (4.70)	38.38 (4.61)	0.001	0.154 (0.968; 0.926 to 1.012)
NLR, median (quartiles)	2.49 (1.73, 3.58)	2.26 (1.64, 3.11)	#0.032	0.510 (1.047; 0.914 to 1.200)
PLR, median (quartiles)	146.68 (117.36, 206.66)	145.08 (111.37, 189.81)	#0.211	0.785 (0.999; 0.996 to 1.003)
Postoperative				
Hemoglobin, median (quartiles), g/L	108.00 (97.00, 121.00)	113.00 (101.00, 124.00)	#0.004	
Albumin, median (quartiles), g/L	29.75 (26.63, 32.83)	30.80 (27.73, 34.08)	#0.002	0.366 (0.979; 0.935 to 1.025)
NLR, median (quartiles)	15.96 (10.20, 23.10)	15.03 (9.95, 22.35)	#0.348	0.182 (1.015; 0.993 to 1.038)
PLR, median (quartiles)	251.50 (173.36, 379.64)	251.70 (172.92, 360.19)	#0.438	0.670 (1.000; 0.998 to 1.001)
Blood Loss, median (quartiles), ml	300.00 (200.00, 400.00)	300.00 (200.00, 400.00)	#0.011	
Duration of Surgery, median (quartiles), min	390.00 (300.00, 470.00)	360.00 (280.00, 435.00)	#0.002	0.372 (1.001; 0.999 to 1.004)
Intraoperative Fluid Infusion, median (quartiles), ml	3000 (2500, 3500)	3000 (2500, 3500)	#0.054	
Intraoperative Fluid Infusion Rate, median (quartiles), ml/(kg×h)	8.09 (6.48, 9.79)	8.17 (6.42, 9.74)	#0.829	0.360 (1.053; 0.943 to 1.176)
Intraoperative RBC Transfusion, median (quartiles), u	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	#0.005	0.042 (1.141; 1.005 to 1.295)
Intraoperative FFP Transfusion, median (quartiles), ml	0.0 (0.0, 200.0)	0.0 (0.0, 0.0)	#0.008	
Intraoperative Urine Output, median (quartiles), ml	750.0 (500.0, 1000.0)	700.0 (400.0, 1000.0)	#0.062	0.277 (1.000; 1.000 to 1.001)
Fluid Infusion over 24 hr, median (quartiles), ml	4270 (3500, 5030)	4150 (3500, 4800)	#0.173	
Fluid Infusion Rate over 24 hr, median (quartiles), ml/(kg×h)	2.97 (2.44, 3.68)	2.83 (2.35, 3.45)	#0.042	0.888 (1.022; 0.754 to 1.386)
Postoperative ICU Admission, No. (%)	33 (9.7)	9 (3.0)	0.001	0.078 (0.445; 0.181 to 1.093)
Reoperation, No. (%)	35 (10.3)	4 (1.3)	<0.001	<0.001 (0.110; 0.038 to 0.323)
Vasopressor Administration, No. (%)	75 (22.1)	71 (23.4)	0.695	0.540 (1.138; 0.753 to 1.720)

PLOS, prolonged length of stay; OR, Odds Ratio; 95% CI, 95% confidence interval; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; RBC, red blood cell; FFP, free-frozen plasma; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte- to-monocyte ratio. Variables in the multivariable analysis were selected by collinearity diagnostics. # indicates that the Mann-Whitney U test was utilized.

D; [Supplementary Figures S1C, D](#)). Furthermore, age, smoking status, preoperative albumin level, postoperative hemoglobin level and postoperative reoperation demonstrated consistent predictive effects across all four models ([Figure 2](#)).

In our study, the accuracy of the predictive models was evaluated using ROC curves ([Figure 3](#)) and confusion matrix ([Supplementary Figure S2](#)). Comparisons were made between the random forest and xgboost models developed using both quantified intraoperative circulation data and manual intraoperative circulation assessments. The results indicated that the quantified data prediction models (the AUROC for Model 1 and Model 2 were 0.756 [95% CI, 0.682–0.831] and 0.801 [95% CI, 0.733–0.869], and the OA were 71.25% and 68.75% respectively) ([Figures 3A, B](#); [Supplementary Figures S2A, B](#)) exhibited higher AUROC values

and OA compared to the prediction models based on manual assessments (the AUROC for Model 3 and Model 4 were 0.719 [95% CI, 0.641–0.797] and 0.705 [95% CI, 0.624–0.786], and the OA were 63.13% and 65.00% respectively) ([Figures 3C, D](#); [Supplementary Figures S2C, D](#)).

3.5 Real-time manner of quantified intraoperative circulation data predictive model

Apart from their higher accuracy, the quantified intraoperative circulation data models also demonstrated a real-time prediction capability. [Figure 4](#) showcases the performance of a real-time

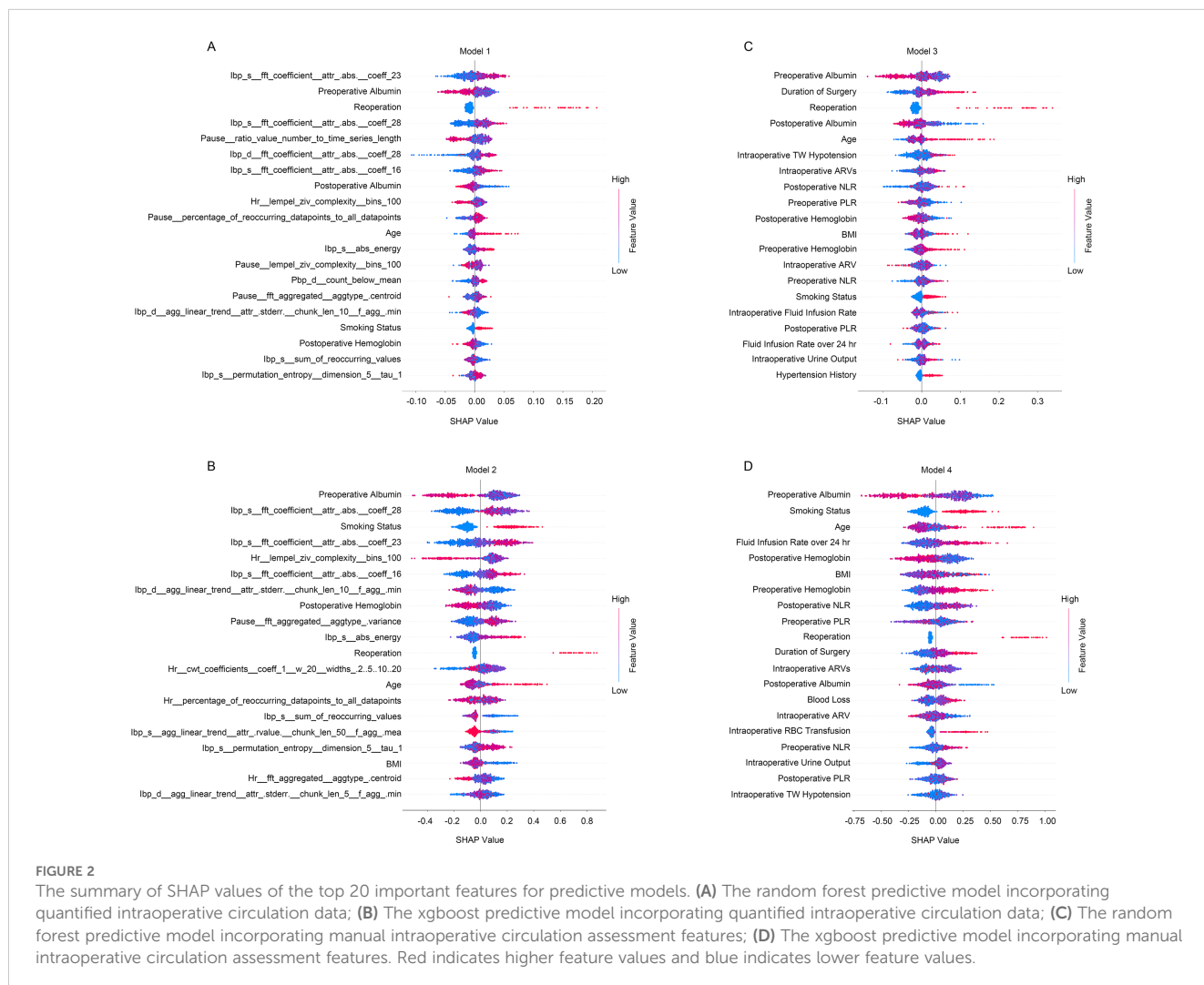
prediction system based on the prediction score using the xgboost predictive model with quantified intraoperative circulation data. At intervals of every 5 minutes, the circulation data including heart rate, pulse, systolic and diastolic blood pressure were recorded for randomly selected patients (Figure 4A). With the accumulation of intraoperative circulation data, the features of intraoperative circulation data extracted using machine learning algorithms changed dynamically. Therefore, subsequently, these data inputs were used to generate prediction probability scores for postoperative outcomes in real time (Figure 4B). This dynamic approach allows for timely monitoring and assessment of patient risk throughout their surgical process.

4 Discussion

In this study, we utilized machine learning algorithms (Fourier transform, ricker wavelet, etc.) to analyze intraoperative circulation time series data and extract relevant features. Based on quantified intraoperative circulation data and other perioperative clinical factors, our research developed and validated real-time predictive models for PLOS after head and neck surgery with free flap

reconstruction. The implementation of these models not only enables clinicians to identify high-risk patients susceptible to PLOS but also offers a potential method for evaluating and optimizing management strategies during free flap reconstruction.

Previous research has focused on understanding the relationship between intraoperative circulation state and postoperative prognosis (9, 15, 24). However, most studies have primarily focused on a single circulation indicator, such as intraoperative blood pressure, while overlooking the complexity of irregular time series data associated with intraoperative circulation. The high variability in these datasets poses challenges in identifying relevant features through manual methods. Advancements in machine learning and neural network algorithms offer new opportunities for feature extraction and analysis of time series data (23, 25). Therefore, our study addresses this challenge by utilizing machine learning algorithms to extract features from intraoperative circulation and assess their impact on PLOS after free flap reconstruction. Among numerous algorithms employed for intraoperative circulation data quantification, Fourier transform and wavelet analysis captured global and localized frequency patterns, while complexity and entropy measures provided insights into the structural and



dynamic properties of the data. The combination of these algorithms enables a comprehensive analysis of intraoperative circulatory data.

While machine learning algorithms have proven effective in extracting features (114 features) from intraoperative circulation data, challenges persist in interpreting these features and optimizing intraoperative circulation management strategies during head and neck surgery with free flap reconstruction (23). To address this issue, the current study developed individualized predictive models using quantified intraoperative circulation data and other relevant perioperative clinical factors through machine learning algorithms (random forest and xgboost). Along with the accumulation of intraoperative circulation data, the features of quantified intraoperative circulation data varied accordingly. Dynamic changes in patients' indices of quantified intraoperative circulation data provided the potential for predictive models that comprise these indices to dynamically assess the impact of

intraoperative circulation on postoperative PLOS. Therefore, real-time prediction scores offered by these models during free flap reconstruction may serve as valuable references for clinicians to refine their intraoperative circulation management and potentially mitigate the occurrence of PLOS after free flap reconstruction.

To evaluate the predictive capabilities of two different intraoperative circulation data evaluation approaches, we developed predictive models by combining features from manual intraoperative circulation assessments with other relevant perioperative clinical factors using machine learning algorithms (random forest and xgboost). The prediction models based on quantified intraoperative circulation data demonstrated superior performance in terms of AUROC and OA when compared to the models solely relying on manual intraoperative circulation assessments. Our findings suggest that features extracted and selected from intraoperative circulation data through machine learning algorithms not only enable real-time predictions for

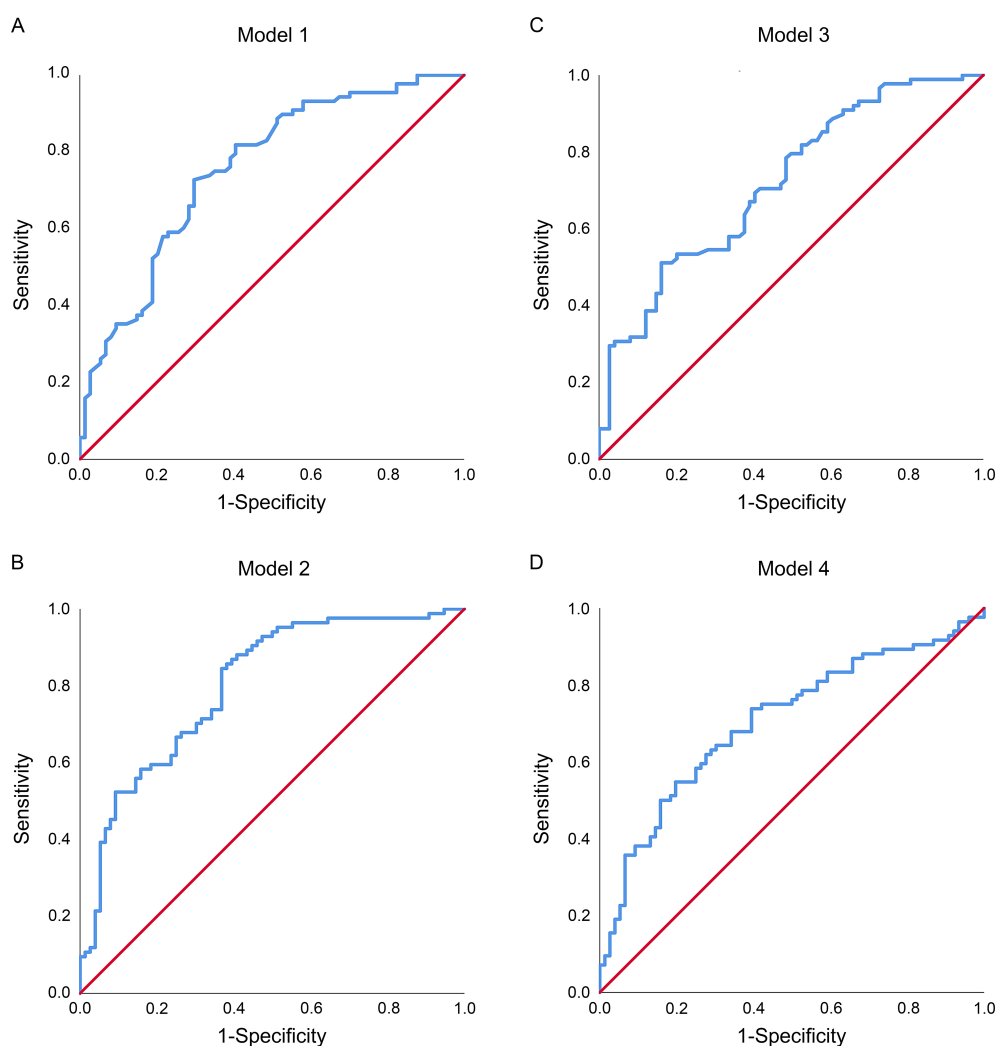


FIGURE 3

The receiver operating characteristic (ROC) curves of predictive models in the validation cohorts. (A) The random forest predictive model incorporating quantified intraoperative circulation data; (B) The xgboost predictive model incorporating quantified intraoperative circulation data; (C) The random forest predictive model incorporating manual intraoperative circulation assessment features; (D) The xgboost predictive model incorporating manual intraoperative circulation assessment features.

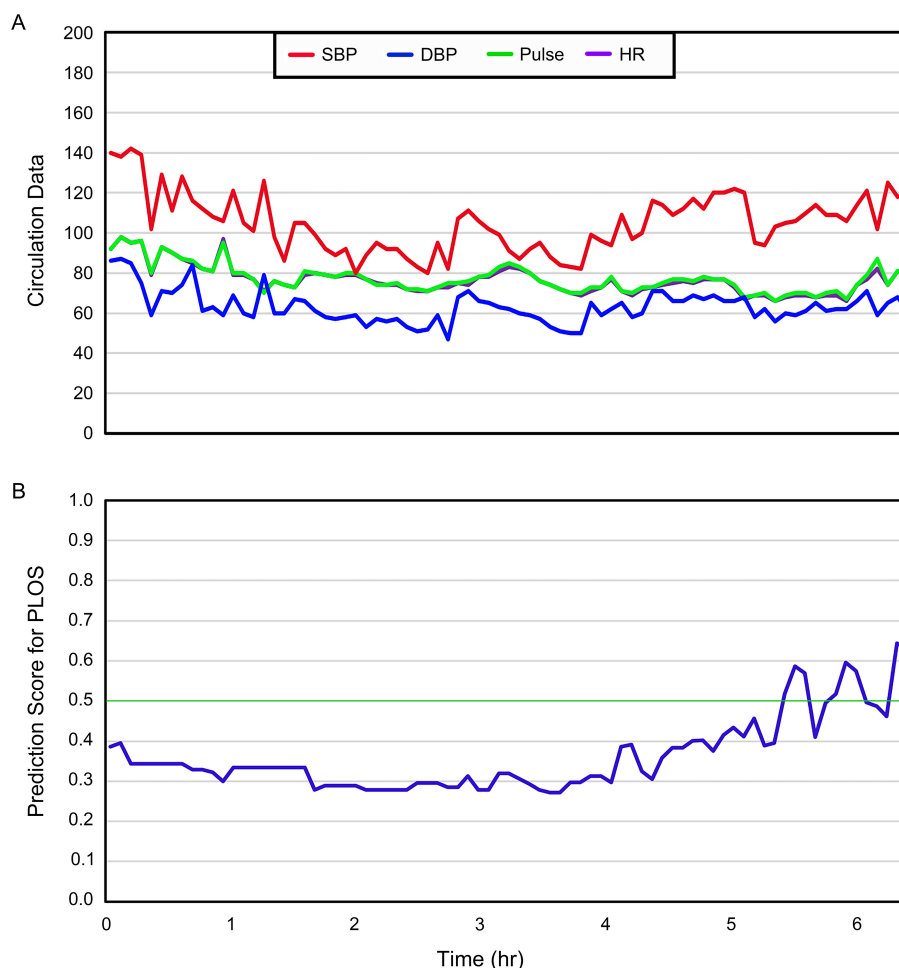


FIGURE 4

The performance of the real-time prediction system that based on the prediction score for the quantified intraoperative circulation data xgboost prediction model of a randomly selected patient. (A) The recorded intraoperative circulation data of the patient, including pulse, heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP); (B) The real-time prediction scores derived from intraoperative circulation data through machine learning algorithms.

PLOS following head and neck surgery with free flap reconstruction, but also offer a more comprehensive approach to intraoperative circulation management assessment.

Incorporating manual intraoperative circulation assessments into the predictive models showed intraoperative TW hypotension, AVR and AVRs as independent predictors of PLOS following free flap reconstruction, aligning with previous research emphasizing the impact of intraoperative hypotension on complications and the association of intraoperative MAP variability with adverse events (9, 14, 26). Although their predictive effect was relatively lower compared to quantified intraoperative circulation data, our results underscore the importance of minimizing severe intraoperative hypotension and MAP variability during head and neck surgery with free flap reconstruction.

Independent risk factors (smoking status, intraoperative RBC transfusion and postoperative reoperation) were determined for PLOS following free flap reconstruction. And variables like age, smoking status, preoperative albumin level, postoperative

hemoglobin level and postoperative reoperation exhibited predictive effects on PLOS during modeling. Demographic characteristics (age and smoking status) and postoperative reoperation impacted postoperative short-term prognoses (27, 28). Besides, our prior work established robust links between intraoperative RBC transfusion, perioperative nutrient level and the occurrence of complications and PLOS following fibular flap reconstructions (29–31). Integrating these variables boosted the models' predictive strength, underscoring their essential role in precise PLOS prediction.

Several limitations should be acknowledged in our study. Firstly, as with retrospective analyses, the possibility of unaccounted confounders exists. Secondly, the 5-minute interval of collected intraoperative circulation data might not capture important fluctuations, impacting our analysis. Thirdly, dividing patients into primary and validation cohorts to create predictive models led to reduced sample size. Lastly, while numerous machine learning and deep learning algorithms exist for time series analysis, their application to predict intraoperative circulation data's

influence on PLOS warrants further exploration. In light of these limitations, future research endeavors should focus on prospective studies with larger sample sizes and employ more robust machine learning or deep learning algorithms to better forecast the likelihood of PLOS based on perioperative variables after free flap reconstruction.

This study used machine learning algorithms to extract intraoperative circulation data characteristics and create real-time personalized predictive models for PLOS following head and neck surgery with free flap reconstruction. Our results provide new insights into assessing the connection between intraoperative circulation management and adverse events and suggest possibilities for enhancing intraoperative circulation management through real-time prediction scores. Moreover, our predictive models integrated intraoperative circulation data features and clinical risk factors, ensuring precise estimation of a patient's PLOS development likelihood.

Data availability statement

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

Ethics statement

The studies involving humans were approved by The Institutional Review Board (IRB) of Sun Yat-sen Memorial Hospital, Sun Yat-sen University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The retrospective nature of this study.

Author contributions

ZL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Writing – original draft. JW: Data curation, Formal analysis, Project administration, Software, Visualization, Writing – original draft. YC: Data curation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft. BZ: Supervision, Validation, Visualization, Writing – review &

editing. MC: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. MG: Conceptualization, Methodology, Project administration, Software, Supervision, Validation, Writing – review & 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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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2024.1473447/full#supplementary-material>

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Case Report: Complete response to four cycles of camrelizumab in a PD-L1 negative patient with advanced oral squamous cancer

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Immunotherapy has brought better survival benefits in the treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, owing to the lack of relevant biomarkers that could predict the efficacy of this treatment, it often has to be maintained. Here we report on a patient with stage IVA squamous cell carcinoma of the tongue who developed an unresectable lesion in the neck after surgery and radical chemoradiotherapy. After four cycles of intermittent immunotherapy with camrelizumab, complete response (CR) was achieved. Next-generation sequencing showed that the TP53/FANCA/FAT1 gene mutations and negative PD-L1 expression were involved. The patient has been followed up for 4 years without R/M. This situation has not been reported previously, suggesting that some patients can benefit from short-term immunotherapy and even achieve CR; moreover, there may be more molecular markers to be discovered that can predict the efficacy of immunotherapy. We can conduct in-depth research on relevant molecular markers, formulate personalized immunotherapy strategies and plans, and facilitate the development of new precision treatment strategies for HNSCC.

KEYWORDS

immunotherapy, complete response, unresectable recurrent or metastatic squamous cell carcinoma, gene mutation, camrelizumab, case report

Introduction

Oral cancer is one of the most common malignant tumors of head and neck squamous cell carcinoma (HNSCC). The incidence rate of tongue SCC among oral cancers is 25–40% (1). Postoperative radiotherapy combined with chemotherapy can achieve better local control and overall survival (OS) rates for locally advanced tongue SCC (2, 3), but 40% of patients still have recurrences (1). Some patients even develop unresectable R/M disease. R/M HNSCC has a poor prognosis, more than 50% of patients are unable to undergo salvage surgery (4), with a median OS of only 10–15 months (5).

Immune checkpoint inhibitors (ICIs)—compared with traditional chemotherapy, radiotherapy, and targeted therapy—have significantly improved the overall survival rate of some unresectable R/M HNSCCs. In the Updated Results of the Phase III KEYNOTE - 048 Study, the objective response rate of pembrolizumab monotherapy in patients with PD-L1 CPS ≥ 1 was 16.9% (6). Currently, PD-L1 is identified as a molecular marker that can predict the efficacy of immunotherapy; however, there are few others (7). Therefore, it is difficult to define the maintenance time of immunotherapy according to the current statement (8). The usual practice is to continue using the ICIs for 2 years or until clear progression or serious adverse reactions occur. In some patients who have achieved CR or sustained CR during early, mid-term, or maintenance treatment, the medication time may be shortened or the ICIs can be used intermittently, thereby reducing the possibility of immune-related adverse events (irAEs) and unnecessary expense. Given this, future research should screen for stable and effective biomarkers for R/M HNSCC and conduct individualized treatment with short cycles or shortened medication times for some cases with early CR.

Here, we report for the first time a rare case of a patient with unresectable recurrent SCC of the tongue who was negative for PD-L1, had TP53/FANCA/FAT1 gene mutations, and achieved CR after short-term intermittent treatment with camrelizumab.

Case presentation

In November 2016, a 55-year-old man visited the dental department of our hospital because of pain on the right tongue edge for more than 1 month. On November 14, 2016, right tongue resection, partial right mandibular resection, and right cervical lymph node dissection were implemented, along with left forearm flap transplantation for repair. Immunohistochemistry results were as follows: CK5/6 (+), P40 (+), P63 (+), Topo II (20%), Ki-67 (50%), P53 (-), and P16 (-). PD-L1 expression in tumor cells was negative (Figure 1). The patient was diagnosed with well-differentiated SCC

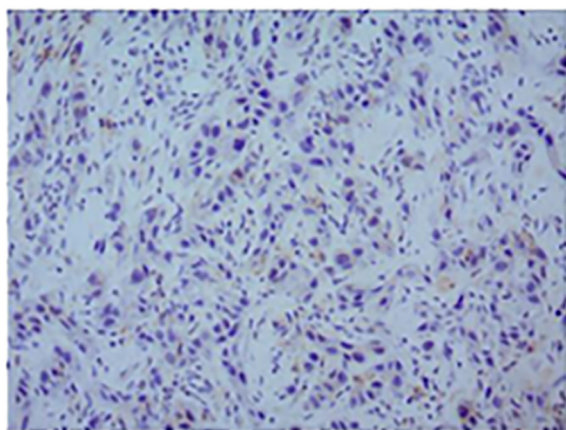


FIGURE 1
Representative micrographs of PD-L1 expression (original magnification, $\times 200$). The positive rate of PD-L1 was less than 1%; the PD-L1 test result was negative.

of the tongue with right cervical lymph node metastasis, and the AJCC TNM stage was cT3N2bM0 IVA.

A total of six rounds of docetaxel 120 mg D1 and oxaliplatin 150 mg D1 (TP) regimen chemotherapy was started on May 24, 2017, during which postoperative radiotherapy was performed simultaneously. And the condition was evaluated as CR according to response evaluation criteria in solid tumors version 1.1 (RECIST v1.1) after treatment.

On May 19, 2019, an MRI scan of the neck showed that the left cervical lymph node was swollen with necrosis. The left neck mass was resected twice, on May 31 and July 26, 2019, and the postoperative pathology showed SCC of the left neck.

On November 24, 2019, another MRI examination showed multiple enlarged and fused lymph nodes in the left side of the neck, some with necrosis, and obvious adhesions between some lymph nodes and the common carotid artery. This condition had progressed more than before (Figure 2A1–8), and it was assessed to be unresectable.

On November 26 and December 31, 2019, two cycles of paclitaxel 400 mg D1, cisplatin 140 mg D1, and Tegafur 40 mg/60 mg D1–14 (TPF), and camrelizumab 200 mg D1 were given. Due to measures to contain the COVID-19 epidemic in Shanghai in early 2020, he could not be readmitted to the hospital, so treatment was postponed.

On April 3, 2020, a neck MRI scan showed that the tumor had significantly improved compared with November 24, 2019 (Figure 2B1–8). He was then treated with camrelizumab 200 mg once in April and again in June 2020. Thereafter, he did not receive immunologic drugs or any other chemotherapy owing to economic constraints.

On June 15, 2020, another MRI scan showed that the lymph node metastasis in the left neck was smaller than before. No abnormally enlarged lymph nodes were found in the reexamination on March 2, 2021, and the treatment effect was evaluated as a CR (Figure 2C1–8). A follow-up MRI on February 15, 2022 showed continued remission (Figure 2D1–8).

A timeline summarizing these events is shown in Figure 3. It has been more than 7 years since the patient first became ill. After treatment for recurrence, he has been regularly followed in our department for more than 4 years. He is in a state of continuous CR, and his current condition is stable. The patient's Next-generation sequencing showed that there were TP53 gene nonsense mutation, FANCA gene frame shift mutation, FAT1 gene missense mutation and that TMB had 7.98 mutations/Mb.

Discussion

Immunotherapy is currently recommended as the first-line treatment for R/M HNSCC. Compared with traditional regimens, it can significantly improve patient survival; however, only 20–30% of the patients benefit (9). There are also few molecular markers that can predict the efficacy of this modality and no standard for its maintenance time. The routine is to maintain it for 2 years or more until disease progression or intolerable toxicity. However, there are no literature reports on short-term medication or on

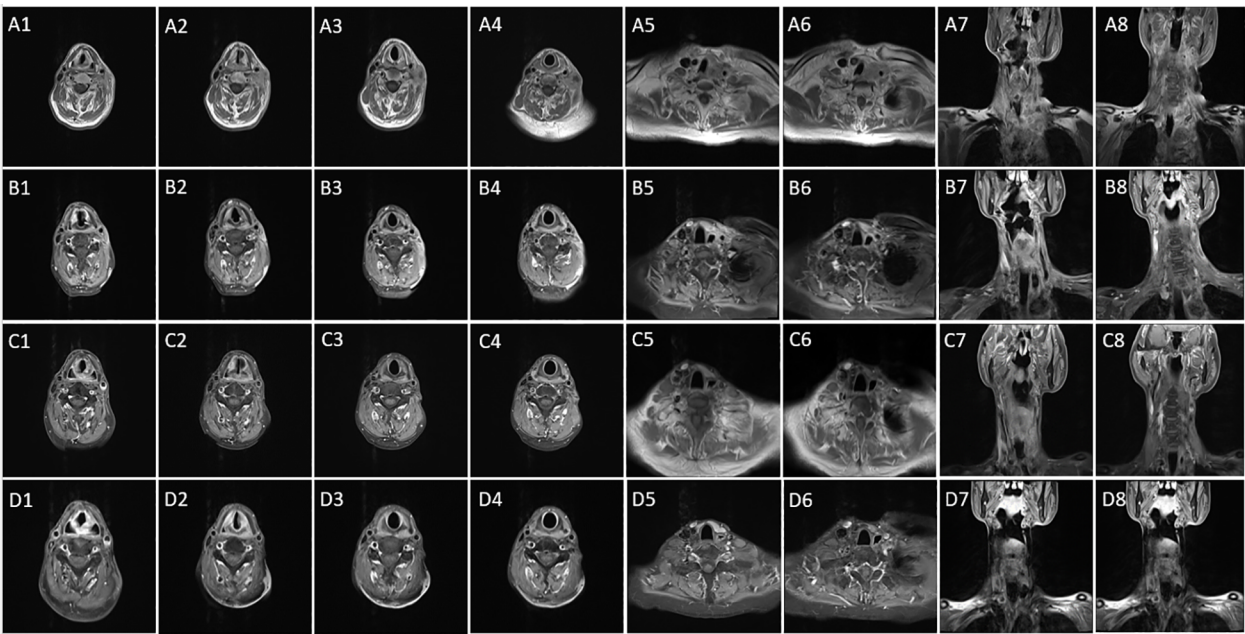


FIGURE 2
(A1–8) This tumor infiltrated the middle and upper neck as well as the base of the neck; the condition is now more advanced than before (November 24, 2019). (B1–8) The disease is close to complete response after four cycles of immunotherapy and two cycles of chemotherapy (April 3, 2020). (C1–8) According to RECIST v1.1 criteria, the patient’s disease is now in complete response (March 2, 2021). (D1–8) The disease remains in complete response (February 15, 2022).

shortening the medication time for individualized treatment according to the patient’s condition. The present article reports for the first time a case of CR achieved by short-term application of camrelizumab in a patient with unresectable locally recurrent HNSCC. The patient was followed up for 4 years without recurrence. He has negative PD-L1 expression and TP53/FANCA/FAT1 gene mutations, suggesting that in addition to PD-L1, these gene mutations may also be important molecular markers for immunotherapy. Short-term, intermittent application of immunotherapy in similar patients may enable them to achieve CR and obtain long-term survival benefits. In addition, large-sample studies can be conducted to verify relevant molecular markers and thus optimize individualized immunotherapy strategies and

protocols. Thus, it may be possible to achieve the same therapeutic effects in R/M HNSCC patients while minimizing irAES and reducing the associated economic burden.

Molecular markers that could predict the efficacy of immunotherapy are currently a research hotspot in the context of precision medicine. In phase III of the KEYNOTE-048 clinical study, the biomarker PD-L1 stratified design was used to optimize the selection of immunotherapy benefit groups. As a result, a significant OS benefit was observed in the patient group with a PD-L1 combined positive score equal to or greater than 20. Furthermore, the 5-year survival rate in such patients ranged from approximately 15% to 20%. Therefore, PD-L1 is currently an effective molecular marker for HNSCC. TP53 is the most

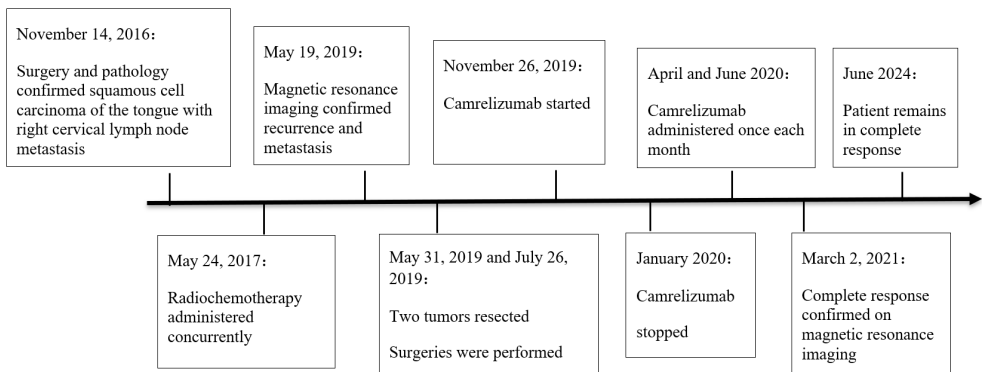


FIGURE 3
Timeline of the patient’s clinical course.

common somatic gene mutation in HNSCC. Once TP53 gene mutated, it will transform from tumor suppressor gene to oncogene. HNSCC patients with the TP53 mutation respond poorly to immunotherapy and chemotherapy (10), as related to the generally poor prognosis of HNSCC. However, a previous study found that HNSCC patients carrying TP53/FAT1 commutations had higher PD-L1 expression levels and longer median survivals than those carrying only TP53 gene mutations (11). Currently, the regulatory mechanism of the FAT1 gene is not completely clear; it is considered to be a tumor suppressor or driver (12). The FAT1 gene mutation is the second most common mutation in HNSCC. It is an important factor in the occurrence and development of HNSCC and an independent predictor of a poor prognosis (13, 14). However, combined with HPV (-) in HNSCC patients, the FAT1 gene mutation is significantly associated with better OS (15). The FANCA gene is a DNA damage repair gene. FANCA gene mutations can change the pathways of cellular energy metabolism, as well as alter DNA stability and lead to mitochondrial functional damage, thereby aggravating the accumulation of DNA damage in HNSCC cell models and exacerbating the disease (16). There is currently no clinical application research related to immunotherapy for HNSCC.

In the face of multiple genetic mutations and potential heterogeneity in HNSCC patients, it seems unrealistic to screen for a single molecular marker to predict the effect of immunotherapy. Multimodal combinations of molecular markers represent opportunities and challenges for predicting the benefits of ICIs and need to be further explored. Our patient with negative PD-L1 expression achieved an astonishing CR with short-term, intermittent immunotherapy, suggesting that his sensitivity to immunotherapy may be related to other molecular markers. Thus, it is important to further explore other potential predictive biomarkers. TP53, FAT1, and FANCA gene mutations revealed by next-generation sequencing suggest that this patient's sensitivity to immunotherapy may stem mainly from mutations in these genes. Currently, we have not seen any reports of patients with negative PD-L1 expression and simultaneous mutations in TP53, FAT1, and FANCA genes who are sensitive to immunotherapy. Therefore, our findings may provide new directions for joint research on immunotherapy-related molecular markers.

In current clinical practice for some patients with unresectable local R/M HNSCC, some domestic and foreign experts recommend continued ICI treatment for these patients when they achieve clinical CR with no serious adverse reactions. It is often difficult for head and neck oncologists as well as patients to choose the discontinuation points for ICIs. This is an important issue that, in the current era of precision treatment of head and neck tumors, needs to be solved urgently. The discovery of relevant molecular markers, especially those with TP53/FANCA/FAT1 gene mutations, in this case report may suggest that short-term, intermittent immunotherapy may achieve long-term survival benefits in some patients with R/M HNSCC, and make it possible to personalize immunotherapy while also minimizing irAEs and reducing the patients' economic burden. We reviewed the literature and found that there were no other reports of such cases. Our results may provide new clues for the study of molecular markers in immunotherapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

Ethics statement

The present study complies with the internationally accepted ethical standards. According to local regulations, this study did not require Institutional Review Board approval or consent to participate. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin. 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

JH: Resources, Writing – original draft. GY: Supervision, Writing – review & editing. YM: Methodology, Writing – review & editing. XS: Visualization, Writing – review & editing. YG: Data curation, Supervision, Visualization, Writing – review & editing. HZ: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. MZ: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. CZ: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – review & 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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Allergic history and responses to immunotherapy in individuals with recurrent or metastatic head and neck squamous cell carcinoma

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Objective: To elucidate the association between allergy history and response to immune checkpoint inhibition (ICI) in recurrent or metastatic head and neck squamous cell carcinoma (RM/HNSCC).

Methods: Patients receiving ICI treatment for RM/HNSCC were retrospectively enrolled and classified into two groups based on their previous allergy history. The primary outcome variable assessed was the response to ICI.

Results: A total of 157 patients were included, of whom 27 reported a history of allergies. In multivariate analysis, patients with allergies exhibited an odds ratio of 2.78 [95% confidence interval: 1.54-5.99], significantly surpassing that of the non-allergic group. Other independent predictors of ICI benefit included current smoking status and the primary tumor site being in the oropharynx or hypopharynx. Neither progression-free survival nor overall survival was adversely affected by prior allergy history or smoking status or HPV status or PD-L1 expression.

Conclusion: A prior history of allergies is associated with an enhanced response to immunotherapy in patients with RM/HNSCC.

KEYWORDS

head and neck squamous cell carcinoma, immunotherapy, allergy, smoking, clinical response

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy among all solid cancers, involving more than 850,000 cases annually in the world (1). The immutable risk factors for HNSCC encompass smoking, alcohol consumption, betel nut chewing, and human papillomavirus (HPV) infection.

Additionally, the immune system's response has emerged as a novel risk factor for HNSCC. Numerous studies have probed the relationship between allergic manifestations of the immune response and cancer risk, including pancreatic and prostate cancers (2). Individuals with pronounced atopic tendencies exhibit a heightened propensity to develop allergies, attributable to their exaggerated immune responses to specific environmental antigens. These individuals possess a genetic predisposition to produce elevated levels of immunoglobulin E (IgE) against common allergens. The cross-linking of IgE on the surfaces of particular leukocytes can precipitate allergic disorders such as allergic rhinitis, atopic dermatitis, asthma, and other allergic reactions, including food allergies (3).

The deleterious impact of allergies on cancer development has been elucidated through various hypotheses, with the “prevention hypothesis” and the “immune surveillance hypothesis” being the most prominent. According to the immune surveillance hypothesis, the incidence of allergies is attributed to an overactive immune system that efficiently eradicates malignant cells, thereby diminishing the risk of cancer. Conversely, the prevention hypothesis posits that allergic symptoms are instigated by the swift action of toxins, microorganisms, and environmental particulates that carry or contain carcinogens. Furthermore, allergic symptoms can deter individuals from exposure to perilous environments (4). In the case of glioma and pancreatic cancer, both of which are associated with well understood environmental risk factors, evidence has consistently demonstrated that allergies exert a protective effect (5), but role of allergies on HNSCC seem less reliable.

Even following curative interventions, a significant proportion—30% or more—of patients with HNSCC are susceptible to recurrence. In this context, immune checkpoint inhibition (ICI) has emerged as a beacon of hope, representing a promising therapeutic avenue. Markers such as PD-L1, PD-1, CTLA-4, p53, and tumor mutational burden have been identified as potential factors that may augment the efficacy of treatment, thereby enhancing clinical outcomes for affected patients (6).

While the interconnection between allergic conditions and the incidence of HNSCC has been extensively investigated (7, 8), the interplay between allergies and the efficacy of immunotherapy in patients with HNSCC remains an enigma. The objective of this study is to elucidate the association between the allergy history reported by patients with recurrent or metastatic HNSCC and their subsequent response to ICIs.

Patients and methods

Ethical considerations

This study was approved by the Zhengzhou University Institutional Research Committee. All participants provided written informed consent at initial treatment for medical research. All procedures involving human participants were conducted according to the principles of the Declaration of Helsinki.

Study design

To achieve our objective, we conducted a retrospective review of patients treated with isolated PD-1/PD-L1 or CTLA-4 inhibitors—including pembrolizumab, nivolumab, ipilimumab, or durvalumab—for unresectable recurrent or metastatic HNSCC between January 1, 2020, and December 2023. Patients were excluded from the analysis if they met any of the following criteria: individuals with primary HNSCC; patients who had succumbed to their illness or were lost to follow-up prior to receiving post-treatment imaging to assess clinical response; individuals under the age of 18; and those with an unknown primary tumor. Baseline data pertinent to immunotherapy encompassed the following: treatment commencement date, patient age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) performance score, self-reported allergy history, tumor status determination concerning HPV through p16 analysis via immunohistochemical examination or *in situ* hybridization, and the primary tumor location, prior treatment.

Variable definition

Histopathological slides were meticulously examined by at least two experienced pathologists specializing in head and neck pathology. Current smokers were defined as individuals who consistently consumed a minimum of 20 cigarettes daily for at least one year, without significant cessation periods. Former smokers were classified as those who had quit smoking for no less than two years, while never smokers referred to individuals who had never engaged in smoking (9). The combined positive score (CPS) was defined as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, then multiplied by 100 based on the 22C3 platform (10). Data on allergy history were obtained via self-reported information that included drug allergies, food allergies, and environmental allergies.

Statistical analysis

The primary outcome variable was the response to immunotherapy, determined based on the RECIST guidelines. Patients were classified as having a clinical response to immunotherapy if they exhibited either a complete or partial response; conversely, patients with stable or progressive disease following ICI treatment were categorized as non-responders. Throughout the efficacy assessment phase, ICI were administered continuously until disease progression was observed or until such time as the toxicity became intolerable. The efficacy was determined in accordance with the most favorable response recorded over the entire treatment period, as ascertained through CT and MRI scans, which were conducted at intervals of 3 to 6 months (11). Secondary outcome variables included progression-free survival (PFS) and overall survival (OS).

In the assessment of the primary outcome, potential influencing factors were initially scrutinized through the application of the Chi-square test. Subsequently, those variables that demonstrated statistical significance were subjected to further examination via multivariable logistic regression analysis, with the results presented in terms of odds ratios (ORs) and 95% confidence intervals (CIs). For the secondary outcome, a comparative analysis of clinicopathologic variables between the allergy and non-allergy groups was conducted using the Chi-square test. Following this, patients were meticulously matched in a 1:1 ratio across the two groups by calculating the propensity scores for those variables that were found to be statistically significant. The impact of allergy history on PFS and OS was then analyzed within the matched cohort employing the Kaplan-Meier method. All statistical analyses were performed utilizing R version 3.4.3, with a p-value threshold of less than 0.05 deemed indicative of statistical significance.

Results

Baseline data

A total of 157 patients were enrolled in the study, comprising 123 males and 34 females, with a mean age of 60 ± 11 years. Body Mass Index (BMI) was classified as follows: 69 patients (43.9%) had a BMI of less than 18.5, 72 patients (45.9%) fell within the range of 18.5–23.9, and 16 patients (10.2%) had a BMI of 24.0 or greater. Smoking status was recorded, revealing that 43 patients (27.4%) were current smokers, 96 patients (61.1%) were former smokers, and 18 patients (11.5%) had never smoked. The primary tumor sites included the oral cavity in 37 patients (23.6%), the oropharynx in 46 patients (29.3%), the larynx in 22 patients (14.0%), and the hypopharynx in 52 patients (33.1%). Among the cohort, 10 patients tested positive for HPV. Notably, 28 patients (17.8%) exhibited a CPS of less than 1, while 62 patients (39.5%) had a CPS exceeding 20.

Of the 157 patients, 27 (17.2%) had a documented history of allergies, which appeared to correlate significantly with smoking status ($p=0.029$); however, there were no notable differences in demographic or pathological variables between the allergy and no-allergy groups (all $p>0.05$, as detailed in Table 1). Subsequently, the smoking status factor was incorporated into propensity score calculations with a 1:1 ratio, resulting in the enrollment of 54 patients (27 from each group) for survival analysis (Table 2).

Predictors for immunotherapy response

A complete or partial response to immunotherapy was achieved in 38 patients (24.2%). Among the 27 patients with a history of allergies, a clinical response was observed in 37.0% of this population, which was significantly higher than that of the no-allergy group ($p=0.014$). The clinical response rates were recorded as 34.8% for current smokers, 22.9% for former smokers, and a mere 5.6% for never smokers; this variation was statistically

significant ($p=0.046$). Oral cancer predicted a clinical response rate of 13.5%, while the frequency was 21.7% for oropharyngeal cancer and 18.2% for laryngeal cancer, all exhibiting significantly lower response rates compared to hypopharyngeal cancer, which had a response rate of 36.5% ($p=0.064$). Furthermore, 50% of HPV-positive patients achieved clinical response, suggesting a trend towards higher responsiveness compared to the negative cohort ($p=0.063$). All these factors were further scrutinized in multivariable analysis. Clinical response showed no significant association with other variables (Table 3).

In logistic regression analysis, patients with allergies demonstrated an odds ratio (OR) of 2.78 [95%CI: 1.54–5.99], which was significantly elevated compared to the no-allergy group ($p<0.001$). When compared to never smokers, former smokers exhibited a comparable OR (95% CI: 0.95–2.87), whereas current smokers demonstrated a significantly increased OR of 2.01 (95% CI: 1.36–3.00). Both oral and laryngeal cancers displayed similar ORs, while oropharyngeal and hypopharyngeal cancers were more likely to benefit from immunotherapy, with ORs of 1.47 (95% CI: 1.12–2.36) and 2.98 (95% CI: 1.14–4.87), respectively. HPV status did not significantly influence the likelihood of achieving a clinical response (Tables 4).

PFS and OS

During the median follow-up period of 14 months (range: 4–40), all patients experienced disease progression, leading to the death of 132 individuals. Following the implementation of propensity score matching, no statistically significant disparities were observed in either PFS ($p=0.801$) or OS ($p=0.121$) between patients with and those without a history of allergies. Additionally, neither smoking status nor CPS or HPV status exerted a discernible influence on PFS or OS. However, the primary anatomical sites demonstrated a significant impact on both PFS and OS, with tumors originating in the hypopharynx or oropharynx portending the most dire prognostic outcomes, as illustrated in Figures 1 and 2.

In the whole cohort, the sole independent prognostic factor identified was the primary tumor site; when compared to patients afflicted with oral carcinoma, those presenting with squamous cell carcinoma of the oropharynx and hypopharynx demonstrated a markedly inferior PFS and OS (Tables 5, 6).

Discussion

This study reveals a significant correlation between allergy history and the response to ICI in patients with recurrent or metastatic HNSCC. To the best of the author's knowledge, this research represents a pioneering effort in the literature to explore this specific association. Traditional biomarkers for immunotherapy, such as tumor mutation burden and PD-L1 expression in lung tumors, have been established; however, the prognostic value and applicability of PD-L1 in HNSCC remain unproven. Moreover, assessing mutation burden is often impeded

TABLE 1 Baseline data of the enrolled patients.

Variable	Overall (n=157)	Allergy group (n=27)	No-allergy group (n=130)	p*
Age				
≤60	60 (38.2%)	10 (37.0%)	50 (38.5%)	0.890
>60	97 (61.8%)	17 (63.0%)	80 (61.5%)	
Sex				
Male	123 (78.3%)	21 (77.8%)	102 (78.5%)	0.937
Female	34 (21.7%)	6 (22.2%)	28 (21.5%)	
BMI				
~18.4	69 (43.9%)	10 (37.0%)	59 (45.4%)	0.277
18.5-23.9	72 (45.9%)	12 (44.4%)	60 (46.2%)	
24.0+	16 (10.2%)	5 (18.5%)	11 (8.5%)	
Smoking				
Current	43 (27.4%)	5 (18.5%)	38 (29.2%)	0.029
Former	96 (61.1%)	15 (55.6%)	81 (62.3%)	
Never	18 (11.5%)	7 (25.9%)	11 (8.5%)	
Site				
Oral	37 (23.6%)	7 (25.9%)	30 (23.1%)	0.990
Oropharynx	46 (29.3%)	8 (29.6%)	38 (29.2%)	
Larynx	22 (14.0%)	4 (14.8%)	18 (13.8%)	
Hypopharynx	52 (33.1%)	8 (29.6%)	44 (33.8%)	
HPV status				
Positive	10 (6.4%)	2 (7.4%)	8 (6.2%)	0.808
Negative	147 (93.6%)	25 (92.6%)	122 (93.8%)	
CPS^				
~0.9	28 (17.8%)	4 (14.8%)	24 (18.5%)	0.886
1-20	67 (42.7%)	11 (40.7%)	56 (43.1%)	
21+	62 (39.5%)	12 (44.4%)	50 (38.5%)	
ECOG performance score [#]				
0-1	130 (82.8%)	22 (81.4%)	108 (83.1%)	1.000
2	27 (17.2%)	5 (18.6%)	22 (16.9%)	
Prior treatment [†]				
S	19 (12.1%)	3 (11.1%)	16 (12.3%)	0.833
CRT	36 (22.9%)	8 (29.6%)	28 (21.5%)	
S+R	48 (30.6%)	8 (29.6%)	40 (30.8%)	
S+CRT	54 (34.4%)	8 (29.6%)	46 (35.4%)	
Immunotherapy type				
Pembrolizumab	127 (80.9%)	20 (74.1%)	107 (82.3%)	
Nivolumab	17 (10.8%)	4 (14.8%)	13 (10.0%)	

(Continued)

TABLE 1 Continued

Variable	Overall (n=157)	Allergy group (n=27)	No-allergy group (n=130)	p*
Immunotherapy type				
Ipilimumab	7 (4.5%)	2 (7.4%)	5 (3.8%)	0.814
Durvalumab	6 (3.8%)	1 (3.7%)	5 (3.8%)	

*comparison between allergy and no-allergy groups.
^CPS, combined positive score.
#ECOG, Eastern Cooperative Oncology Group.
!S, surgery; CRT, chemoradiotherapy; R, radiotherapy.

TABLE 2 Baseline data of the enrolled patients after propensity Score Matching.

Variable	Allergy group (n=27)	No-allergy group (n=27)	p*
Age			
≤60	10 (37.0%)	11 (40.7%)	0.780
>60	17 (63.0%)	16 (59.3%)	
Sex			
Male	21 (77.8%)	20 (74.1%)	0.750
Female	6 (22.2%)	7 (25.9%)	
BMI			
~18.4	10 (37.0%)	12 (44.4%)	0.834
18.5-23.9	12 (44.4%)	10 (37.0%)	
24.0+	5 (18.5%)	5 (18.5%)	
Smoking			
Current	5 (18.5%)	5 (18.5%)	1.000
Former	15 (55.6%)	15 (55.6%)	
Never	7 (25.9%)	7 (25.9%)	
Site			
Oral	7 (25.9%)	7 (25.9%)	1.000
Oropharynx	8 (29.6%)	8 (29.6%)	
Larynx	4 (14.8%)	4 (14.8%)	
Hypopharynx	8 (29.6%)	8 (29.6%)	
HPV status			
Positive	2 (7.4%)	2 (7.4%)	1.000
Negative	25 (92.6%)	25 (92.6%)	
CPS^			
~0.9	4 (14.8%)	4 (14.8%)	1.000
1-20	11 (40.7%)	11 (40.7%)	
21+	12 (44.4%)	12 (44.4%)	
ECOG performance score [#]			
0-1	22 (81.4%)	23 (85.2%)	

(Continued)

TABLE 2 Continued

Variable	Allergy group (n=27)	No-allergy group (n=27)	p*
ECOG performance score [#]			
2	5 (18.6%)	4 (4.8%)	1.000
Prior treatment [!]			
S	3 (11.1%)	2 (7.4%)	1.000
CRT	8 (29.6%)	9 (33.3%)	
S+R	8 (29.6%)	7 (25.9%)	
S+CRT	8 (29.6%)	9 (33.3%)	
Immunotherapy type			
	Pembrolizumab	20 (74.1%)	22
(81.5%)			
Nivolumab	4 (14.8%)	3 (11.1%)	0.884
Ipilimumab	2 (7.4%)	1 (3.7%)	
Durvalumab	1 (3.7%)	1 (3.7%)	

*comparison between allergy and no-allergy groups.
^CPS, combined positive score.
#ECOG, Eastern Cooperative Oncology Group.
! S, surgery; CRT, chemoradiotherapy; R, radiotherapy.

by substantial financial costs and prolonged turnaround times for results. In contrast, a patient’s allergy history is readily accessible and easily ascertainable during virtually any clinical interaction. This accessibility enhances the practicality of utilizing allergy history as a predictive tool for immunotherapy response in patients with recurrent or metastatic HNSCC, thereby facilitating informed therapeutic decisions.

Patients exhibiting a clinically beneficial response to immunotherapy were likely to demonstrate a history of allergies, but survival analysis suggests that a history of allergies did not confer a protective effect against disease progression and mortality in patients undergoing ICI treatment for recurrent or metastatic HNSCC. Potential explanations may be multifaceted, encompassing our relatively modest sample size, the inherently aggressive characteristics of recurrent or metastatic HNSCC, as well as other deleterious pathologic attributes. This study substantiates the notion that the response to immunotherapy is influenced by various factors,

TABLE 3 Association between clinicopathologic variables and immunotherapy response.

Variable	Complete or partial response (n=38)	Progressive or stable disease (n=119)	p
Age			
≤60	14 (36.8%)	46 (38.6%)	0.841
>60	24 (63.2%)	73 (61.4%)	
Sex			
Male	32 (84.2%)	91 (76.5%)	0.313
Female	6 (15.8%)	28 (23.5%)	
BMI			
~18.4	16 (42.1%)	53 (44.5%)	0.963
18.5-23.9	18 (47.4%)	54 (45.4%)	
24.0+	4 (10.5%)	12 (10.1%)	
Smoking			
Current	15 (39.5%)	28 (23.5%)	0.046
Former	22 (57.9%)	74 (62.2%)	
Never	1 (2.6%)	17 (14.3%)	
Site			
Oral	5 (13.2%)	32 (26.9%)	0.064
Oropharynx	10 (26.3%)	36 (30.2%)	
Larynx	4 (10.5%)	18 (15.1%)	
Hypopharynx	19 (50.0%)	33 (27.7%)	
HPV status			
Positive	5 (13.2%)	5 (4.2%)	0.063
Negative	33 (86.8%)	114 (95.8%)	
CPS^			
~0.9	4 (10.5%)	24 (20.2%)	0.220
1-20	15 (39.5%)	52 (43.7%)	
21+	19 (50.0%)	43 (36.1%)	
Allergy history			
Yes	11 (28.9%)	16 (12.3%)	0.014
No	27 (71.1%)	114 (87.3%)	
ECOG performance score [#]			
0-1	31 (81.6%)	99 (83.2%)	0.818
2	7 (18.4%)	20 (16.8%)	
Prior treatment [!]			
S	4 (10.5%)	15 (12.6%)	
CRT	10 (26.3%)	26 (21.8%)	
S+R	11 (28.9%)	37 (31.1%)	

(Continued)

TABLE 3 Continued

Variable	Complete or partial response (n=38)	Progressive or stable disease (n=119)	p
Prior treatment [!]			
S+CRT	13 (34.2%)	41 (34.5%)	0.953
Immunotherapy type			
Pembrolizumab	31 (81.6%)	96 (80.7%)	0.836
Nivolumab	3 (7.9%)	14 (11.8%)	
Ipilimumab	2 (5.3%)	5 (4.2%)	
Durvalumab	2 (5.3%)	4 (3.4%)	

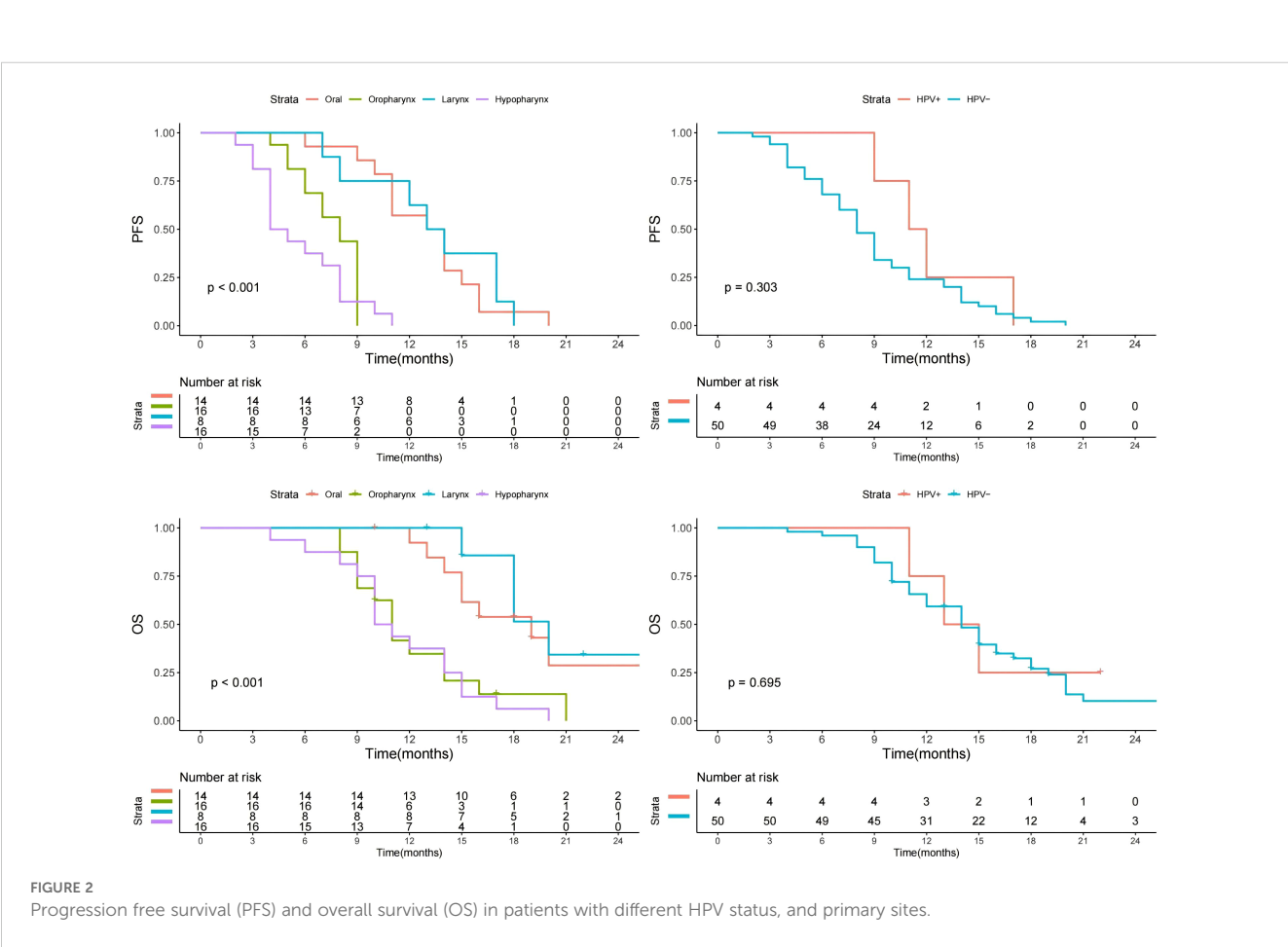
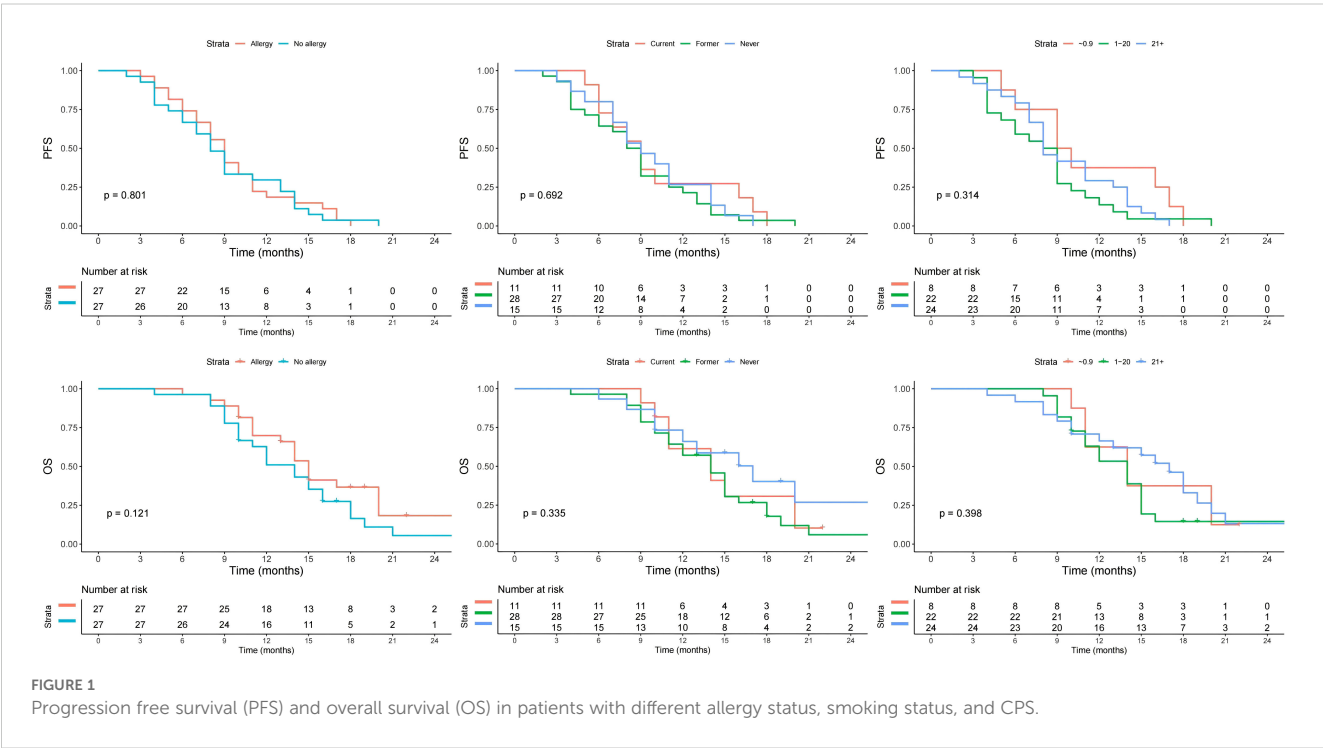
[^]CPS, combined positive score
[#]ECOG, Eastern Cooperative Oncology Group.
[!]S, surgery; CRT, chemoradiotherapy; R, radiotherapy.

including tumor mutation burden, PD-L1 expression, inflammatory gene expression profiles, tumor grading, and pre-treatment nutritional status (12). Each of these variables may embody distinct yet complementary mechanisms that enhance the efficacy of immunotherapy in patients with recurrent or metastatic HNSCC.

Allergies and atopic symptoms are characterized by a systemic enhancement of Th2 immunity, which can potentially fortify antitumor immunity and mitigate cancer risk in allergic individuals (13). This systemic predisposition towards Th2 immunity may also facilitate improved responses to ICI in the context of allergic reactions observed in this study. Moreover, recent advancements have yielded increasing evidence supporting the pivotal role of IL-9 production by

TABLE 4 Logistic analysis of the association between clinical pathologic variables and immunotherapy response.

Variable	OR [95%CI]	p
Smoking		
Never	Reference	0.079
Former	1.85 [0.95-2.87]	
Current	2.01 [1.36-3.00]	
Site		
Oral	Reference	0.024
Oropharynx	1.47 [1.12-2.36]	
Larynx	1.37 [0.78-1.98]	
Hypopharynx	2.98 [1.14-4.87]	
HPV status		
Positive	Reference	0.391
Negative	1.28 [0.47-1.75]	
Allergy history		
No	Reference	<0.001
Yes	2.78 [1.54-5.99]	



CD4⁺ T helper cells (Th9) in mediating anti-tumor immunity, particularly in melanoma (14). A study involving 46 patients found early elevations of Th9 cell counts in melanoma patients treated with nivolumab correlated with clinical improvement. Additionally, both IL-9 and IL-31-producing CD4⁺ T cells were upregulated in patients with respiratory, food, and skin allergies. It remains to be determined whether patients with allergies experience a more pronounced increase in Th9 cell counts and IL-9 following ICI treatment (15). Future research exploring comparative changes in cytokine levels, immunoglobulin levels, and overall immunity in patients with a history of allergies versus their non-allergic counterparts undergoing ICI treatment for metastatic HNSCC may elucidate the inflammatory mechanisms underlying the enhanced ICI response observed in allergic individuals in this study. Furthermore, investigations targeting melanoma patients undergoing immune checkpoint inhibition have indicated that those who concurrently utilized antihistamines exhibited significantly lower mortality rates compared to those who did not (16). Given that antihistamines are often prescribed to manage allergic symptoms, it is imperative that further studies assess the concurrent use of antihistamines and ICI treatment in both allergic and non-allergic patients to ascertain their combined effects on therapeutic outcomes.

Smoking is a well-established carcinogenic factor for HNSCC and also exerts a significant impact on allergy (17). Prior studies have analyzed the association between smoking and immunotherapy. In a cohort of 962 non-small cell lung cancer patients treated with immunotherapy, a matched analysis within the pembrolizumab group revealed that never smokers had a significantly shorter PFS and a non-significant trend towards reduced OS. Conversely, never smokers demonstrated a significantly longer PFS and OS compared to current and former smokers within the matched chemotherapy cohort. Pooled multivariable analysis confirmed that the interaction term between smoking status and treatment modality was statistically significant concerning objective response rate ($p = 0.0074$), PFS ($p =$

0.0001), and OS ($p = 0.0020$), underscoring the markedly different impacts of smoking status across the two cohorts (18). A recent review (19) evaluating the relationship between smoking status and the efficacy of PD-1/PD-L1 inhibitors compared with conventional agents analyzed 15 qualifying trials involving 9073 patients. Findings indicated that PD-1/PD-L1 inhibitors correlated with prolonged PFS and OS in current and former smokers but not in never smokers, regardless of cancer type, target of experimental agents, or treatment strategy. While the current study did not observe a significant impact of smoking status on survival, there was a notable association between clinical response and smoking. This finding is particularly intriguing; first, only unresectable recurrent or metastatic HNSCC patients were enrolled in the current study, which typically carries a poor prognosis and where only 24.2% of patients derive benefit from immunotherapy (20). Second, similar research, after adjusting for HPV status, revealed that patients with a history of allergies exhibited significantly decreased risk of disease progression and death with ICI compared to their non-allergic counterparts, a difference potentially explained by the former study not clarifying whether salvaged surgery was performed. Third, there existed discrepancies in tumor biology or the immune microenvironment between HNSCC and other malignant neoplasms.

The immune subterfuge and therapeutic resistance exhibited by HPV positive malignant neoplasms have ignited a keen interest in the application of established immunotherapeutic modalities to these carcinomas. ICI represent the most exhaustively evaluated strategy to date, having conducted the most extensive clinical investigation into HPV positive cancers within the realm of HNSCC. Numerous prior clinical trials did not impose restrictions on HPV status, thereby allowing the participation of HPV negative patients, which has complicated the interpretation of the outcomes. In the context of recurrent platinum-resistant HNSCC, the CHECKMATE-141 trial (21), a phase III investigation of monotherapy with nivolumab versus conventional therapy, demonstrated a significant enhancement in the OS rate with nivolumab (hazard ratio of 0.70, with a 1-year survival rate of 36% compared to 16%). The KEYNOTE-040 trial (22), a phase III study comparing pembrolizumab with standard care in the second-line setting of HNSCC, reported analogous enhancements in the OS rate for the pembrolizumab cohort (hazard ratio 0.80, with a 1-year survival rate

TABLE 5 Univariate analysis of factors influencing progression-free survival (PFS) and overall survival (OS) in the whole cohort.

Variable	PFS	OS
Age (>60 vs ≤60)	0.174	0.290
Sex (Male vs female)	0.300	0.467
BMI (24.0+ vs 18.5-23.9 vs ~18.4)	0.190	0.223
Smoking (Current vs Former vs Never)	0.548	0.417
Site (Hypopharynx vs Larynx vs Oropharynx vs Oral)	<0.001	<0.001
HPV status (Negative vs positive)	0.013	0.022
CPS [^] (21+ vs 1-20 vs ~0.9)	0.245	0.307
Allergy history (Yes vs no)	0.742	0.267
ECOG performance score [#] (2 vs 0-1)	0.428	0.175
Prior treatment [!] (S+CRT vs S+R vs CRT vs S)	0.674	0.557

[^]CPS, combined positive score

[#]ECOG, Eastern Cooperative Oncology Group.

[!] S, surgery; CRT, chemoradiotherapy; R, radiotherapy.

TABLE 6 Multivariable analysis of factors influencing progression-free survival (PFS) and overall survival (OS) in the whole cohort.

Variable	PFS		OS	
	HR [95%CI]	p	HR [95%CI]	p
Site				
Oral	ref		ref	
Oropharynx	2.21 [1.13-5.28]	0.003	1.78 [1.08-3.43]	0.009
Larynx	1.40 [0.54-3.31]	0.336	1.36 [0.52-3.21]	0.289
Hypopharynx	3.33 [1.54-7.78]	<0.001	3.55 [1.67-8.45]	<0.001
HPV status				
Positive	ref		ref	
Negative	1.40 [0.64-5.17]	0.276	1.58 [0.43-6.11]	0.327

of 37% versus 26%). Both of these studies encompassed both HPV positive and HPV negative participants. An exploratory subgroup analysis of CHECKMATE-141 suggests that anti-PD-1 therapy may be more efficacious in HPV positive tumors (with a median overall survival of 9.1 months versus 4.4 months, as compared to a median overall survival of 7.5 months versus 5.8 months in HPV negative tumors); however, no such improvement was discerned in the HPV positive subgroup within the KEYNOTE-040 trial. The KEYNOTE-048 trial (23), a phase III randomized study comparing monotherapy with pembrolizumab, combination therapy with pembrolizumab and chemotherapy, and chemotherapy alone in the first-line setting of recurrent/metastatic HNSCC, indicates that pembrolizumab, either as monotherapy or in combination, confers superior outcomes over standard chemotherapy irrespective of HPV status. Collectively, these findings underscore the efficacy of anti-PD-1 agents in HNSCC, albeit the differential impact on HPV positive versus HPV negative tumors remains elusive. In comparison with standard chemotherapy regimens, the augmented sensitivity of both HPV(+) and HPV(-) HNSCC to immune checkpoint blockade may reflect a myriad of distinct mechanisms that foster inflammation and immunogenicity. HPV(+) HNSCC tumors typically exhibit a lower mutational burden; viral antigens serve as potent immunogens, prompting the infiltration of HPV antigen-specific CD8+ T cells. Conversely, HPV(-) HNSCC tumors present with a moderate to high mutational burden, potentially enriching neoantigen-specific CD8+ T cells (24). We did not observe that HPV status imparted a significant influence on the efficacy or prognosis of ICI, though the sample size of HPV(+) HNSCC patients was notably small, necessitating further large-scale studies to elucidate this issue.

The correlation between PD-L1 expression and the efficacy of ICI has been the subject of extensive analysis, yielding conflicting outcomes. Both Scheff et al. (25) and our own investigations failed to observe that a high CPS was predictive of enhanced ICI efficacy. However, in the Checkmate 141 trial (26), employing a threshold of $\geq 1\%$ tumor membrane PD-L1 expression as the criterion for inclusion, nivolumab demonstrated a more pronounced reduction in mortality risk for PD-L1 positive patients compared to standard treatment, whereas PD-L1 negative patients exhibited a mortality risk ratio of 0.89 (95% CI: 0.54-1.45). The most recent analysis (27), conducted following an extended period of follow-up, reveals that the therapeutic benefits of nivolumab for PD-L1 negative patients augment over time, with the mortality risk ratio diminishing to 0.73, while the advantages for PD-L1 expressing patients remain consistent. When compared to the solitary expression of tumor PD-L1 in HNSCC, the incorporation of PD-L1 expression within tumor infiltrating lymphocytes (TIL) yielded a superior predictive efficacy. For instance, a retrospective analysis of patients undergoing pembrolizumab treatment indicated no significant variation in response based on tumor PD-L1 expression alone (defined as $\geq 1\%$). However, when both tumor and TIL PD-L1 expression were considered in tandem, PD-L1 positive HNSCC patients exhibited a significantly enhanced response rate, PFS, and OS (28).

Limitations of the current study must be acknowledged. First, our sample size was relatively small, it might decrease our statistic power. Second, this investigation is grounded in a highly heterogeneous cohort of patients, characterized by diverse

primary tumor localizations. Third, external validation of a large cohort via multicenter studies is warranted before clinical application. Fourth, definition of allergy history was mainly based on self-report, future study should consider objective measures, such as IgE level assessment and skin prick test.

In conclusion, patients exhibiting a clinically beneficial response to immunotherapy were likely to demonstrate a history of allergies, but survival analysis suggested that a history of allergies did not confer a protective effect against disease progression and mortality in patients undergoing ICI treatment for recurrent or metastatic HNSCC. The findings of this research underscore the potential utility of allergy history in predicting immune therapy responses and identifying candidates particularly well-suited for immunotherapy. Additional confirmatory investigations are imperative to delineate the intrinsic mechanism underlying this correlation, including the examination of the functions of Th9 cells, interleukin-9, antihistamines, and other pertinent factors.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Zhengzhou University Institution. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FL: Writing – original draft, Writing – review & editing. YW: Writing – original draft, Writing – review & editing. ZM: Writing – original draft, Writing – review & editing. QZ: Writing – original draft, Writing – review & editing. YC: Writing – original draft, Writing – review & editing. YH: Writing – original draft, Writing – review & 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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Endoscopic surgery versus various open approaches in esthesioneuroblastoma: a systematic review of the literature

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Objective: Esthesioneuroblastoma (ENB) is treated using several open surgery (OpS) methods, with or without endoscopic assistance ($\pm$ E-ass) or endoscopic surgery (ES). This systematic review compared the results with various approaches using OpS $\pm$ E-ass and ES.

Data sources: A systematic PubMed/Medline search was conducted for the period 1990–2023.

Review methods: Keywords were “esthesioneuroblastoma” or “olfactory neuroblastoma” and “surgery,” “surgical,” “resection,” “approach,” “open,” and “endoscopic.” Studies/case series and case reports were included. Results with OpS $\pm$ E-ass (stratified into various approaches) were compared with ES results. Parameters assessed were follow-up period, frequencies of advanced tumor stages, Hyams grade III–IV tumors, negative margins/gross total resection, postoperative complication rates, preoperative/postoperative radiation therapy/chemotherapy, primary tumor progression, and frequency of/time to first recurrence.

Results: A total of 88 studies/case series or single cases/case reports (SC/CR) with results after OpS $\pm$ E-ass (850 cases) and 84 with results after ES (584 cases) were included. Compared with OpS $\pm$ E-ass, after ES, the average follow-up was significantly shorter ($p=0.048$) and mean crude disease-free survival (DFS) significantly better (studies/case series, $p=0.0001$; SC/CR, $p=0.001$). Compared with OpS $\pm$ E-ass, after ES, significantly fewer advanced tumors were treated (studies/case series, $p=0.0001$; SC/CR, $p=0.001$); negative margins were significantly less frequent (studies/case series, $p=0.009$); surgical complications were less frequent (studies/case series, $p=0.022$); less radiation therapy (studies/case series, $p=0.043$) and/or chemotherapy (SC/CR, $p=0.022$) was performed; and recurrences were noted significantly less often (studies/case series, $p=0.0001$; SC/CR, $p=0.034$). Among OpS $\pm$ E-ass, craniofacial resection $\pm$ E-ass showed most significant differences from ES.

Conclusions: These data support that ES can be regarded as the surgical method of first choice in less advanced ENB but may also be a good choice in carefully selected advanced ENB.

KEYWORDS

endoscopic, transcranial, craniofacial, transfacial, open, surgery, esthesioneuroblastoma, olfactorius neuroblastoma

1 Introduction

The treatment for esthesioneuroblastoma (ENB) consists of complete surgical resection and adjuvant therapy (1–9). The literature shows that there has been a shift from open surgery approaches (OpS) to endoscopic surgery (ES). Open bicoronal/transcranial resection (BCR/TCR), craniofacial resection (CFR), and transfacial resection (TFR) were regarded as the gold standard in publications up to the 2000s (10–12). BCR/TCR, CFR, or TFR with endoscopic assistance (BCR/TCR+E-ass, CFR+E-ass, and TFR+E-ass) was introduced in the late 1990s and early 2000s to reduce invasiveness and morbidity (3, 13, 14).

ES has been performed since the beginning of this century, and the results have been published in numerous reports (3, 15, 16). Tumor stage is regarded as a significant prognostic factor, but there is no universally accepted staging system (17, 18). The tumor classification systems proposed by Kadish (19)/Morita (20) and Dulguerov and Calcaterra (21) have most often been assessed. Histopathological classification based on the Hyams grading is now increasingly being recognized as an important prognostic factor (22–24).

The aim of this study was to carry out a literature review to compare the results and outcome in patients undergoing OpS ± E-ass, stratified according to BCR/TCR ± E-ass, CFR ± E-ass, and TFR ± E-ass, and patients receiving ES, relative to known prognostic factors.

2 Methods

A literature review for the period 1990–2023 was performed, using the PubMed/Medline database to search for publications reporting results after surgery for ENB with OpS ± E-ass and ES. The keywords (in the title or abstract each) used were: “esthesioneuroblastoma” OR “olfactory neuroblastoma” AND “surgery” OR “surgical” OR “resection” OR “approach” OR “endoscopic” OR “open.” The systematic review was conducted considering the PRISMA criteria Flow diagram (Figure 1).

Available reviews or meta-analyses were also analyzed for publications cited discussing surgery in pediatric ENB (7), ES (16), OpS (12), and comparisons of OpS ± E-ass and ES (3, 25–27). Besides studies and case series (STUD/CS), also case reports

(CR, summarized together with single cases described in STUD/CS as “SC/CR”) were selected, since many of these describe treatment for advanced ENB and/or ENB associated with specific symptoms and/or unusual locations (28, 29).

Only publications dealing exclusively with ENB and/or that provided sufficient data or results of interest regarding surgical treatment were included. Reports that did not focus on ENB alone but included sufficient and stratified data of interest were also considered. To be suitable for inclusion, STUD/CS had to fulfill criteria (see also the PRISM flow diagram).

Inclusion criteria were in detail: publications published between 1990 and 2023; management of ENB exclusively and/or at least sufficient data regarding tumor histology in publications dealing with various tumors; surgical treatment for ENB with curative intent; publications providing clear definition/stratification of the data relative to the surgical approach, tumor stage/histopathology, and adjuvant therapy; publications that report adequate stratified data regarding follow-up; publications providing adequate follow-up/outcome data/survival data; and publications written in English language or providing an abstract written in English and simultaneously providing adequate data in the abstract. Only the most recent publication was selected if several follow-up reports were published by one group.

Exclusion criteria were in detail: reports that did not provide stratified data regarding the surgical approach or no sufficient data regarding follow-up times or the survival status; publications not dealing with the surgical therapy of ENB; publications dealing with mixed tumors in which no histologically proven ENB could be clearly assigned to the parameters investigated; and publications not written in English language or at least providing an abstract written in English, which includes simultaneously adequate data of interest.

A meticulous review was carried out in all STUD/CS to sample as many as much stratified data of interest as possible, also by calculating these from the materials provided within the reports (e.g., tables).

The parameters of interest assessed in the present study were type of OpS ± E-ass (BCR/TCR ± E-ass, CFR ± E-ass, and TFR ± E-ass) and ES; number of patients operated on, number of conversions from ES to OpS ± E-ass; follow-up period; crude/actuarial survival data; number of patients with advanced tumor-stages (Kadish/Morita and/or Dulguerov and Calcaterra); number of Hyams grade III–IV tumors; frequency of negative margins (NM), gross

total (GTR), or complete resection (CoR: NMs plus GTR); frequency of postoperative complications; frequency/dosage of preoperative and/or postoperative radiation therapy (RT) and/or chemotherapy (ChT); frequency of tumor progression; and first recurrence including time after surgery. Crude/actuarial survival was given as provided in the publications, as overall (OS), disease-specific (DSS), disease-free (DFS), recurrence-free (RFS), progression-free (PFS), and local recurrence-free survival (LRFS).

To indicate how many STUD/CS or SC/CR provided data concerning specific parameters, the term “reports provided data” is used, with the abbreviation “RPD.”

SPSS Statistics for Windows, version 26, was used for analysis (IBM Corporation, Armonk, New York, USA). Although the data in the tables were stratified for TCR/BCR, CFR, or TFR with and without E-ass, all statistical calculations were performed for summarized data regarding TCR/BCR, CFR, or TFR regardless if it was performed with or without E-ass. The average, median, and range of the (mean) values were calculated. Differences/associations between the groups were calculated for continuous and categorical variables using the Mann–Whitney U exact test or chi-square exact test, respectively. A comparison of groups was made if at least five values per group were reported. The significance level was set at $p \leq 0.05$.

3 Results

A total of 144 STUD/CS or CRs, including 1,434 patients, were identified and included in this review (Flow Diagram). Due to the huge number of publications and data, details are summarized in [Supplementary Tables S1–S5B](#).

3.1 Open surgery

A total of 850 patients were extracted out of 88 STUD/CS and CRs selected, published from 1992 to 2023. The results of various OpS $\pm$ E-ass and/or ES procedures were reported in 25 STUD/CS.

3.1.1 BCR/TCR $\pm$ E-ass

A total of 18 STUD/CS or CRs including 96 patients published from 1992 to 2023 were found. BCR/TCR-E-ass was described in eight STUD/CS (2, 30–36), BCR/TCR+E-ass in nine (28, 37–44), and BCR/TCR $\pm$ E-ass was reported in one (45) ([Supplementary Tables S1A, B](#)). Results with other OpS $\pm$ E-ass and/or ES procedures were reported in six STUD/CS (2, 28, 32, 36, 38, 45).

3.1.2 Case series/studies

Seven STUD/CS including 85 patients were published, the mean follow-up times was 53.8 (range 22–84) months. Crude OS was 87.5–100%, DSS 66.7–100%, and DFS 73.3–100% (maximum 5 RPD). Advanced tumors were present in 13.3–100% and in $\geq 50\%$ in four STUD/CS. High-grade tumors were present in 14.3–86.7% (5 RPD). NMs were achieved in 71% (two RPD) and 100%, CoR in 82%–100% (4 RPD). Postoperative complications were observed in

0–42.3% of all cases. RT was administered in 40–100% of patients, with a dose range of 50–65Gy (3 RPD). ChT was performed in 0–33.3% (6 RPD). Primary tumor-progression was reported in one study (6.7%) (2). First recurrence occurred after 1–78 months in 12.5–66.7% of patients (7 RPD), in one report after a mean of 82.1 months (34), and in another >5 years in 29% of the patients (45) ([Table 1a](#); [Supplementary Table 1](#)).

3.1.3 Single cases/case reports

Two single cases were described as part of STUD/CS (32, 38), and nine cases were included in CRs (28, 30, 33, 35, 39, 40, 42–44). The mean follow-up time was 35.7 (range, 6–102) months. Crude OS and DSS rates were 100% each, DFS of 81.8%. Kadish stage C tumors were treated in 90.0% of the patients. A high-grade tumor was described in 16.7% (6 RPD). NMs were achieved in 50% (4 RPD) and CoR in 77.8% (9 RPD). Postoperative complications were observed in 40%, and RT was administered in 90.9% of all cases, with a dosage range of 53.2–60 Gy (5 RPD); 45.5% received ChT. Palliative ChT and biological agents were administered in one CR for regional and distant metastases, which were detected after 2 months, apparently difficult to distinguish from tumor-progression (44) ([Table 1b](#); [Supplementary Table S1](#)).

3.2 CFR $\pm$ E-ass

A total of 49 STUD/CS and CRs including 628 patients, published from 1992 to 2021, were found. CFR-E-ass was evaluated in 35 STUD/CS (18, 21, 22, 46–76), CFR+E-ass in 12 (18, 74, 76–84), and CFR $\pm$ E-ass in two studies (14, 85). Results for CFR and several OpS $\pm$ E-ass and/or ES procedures were reported in 20 STUD/CS (18, 21, 38, 47, 48, 59–61, 63, 65, 66, 68, 71, 72, 74–77, 85).

3.2.1 Case series/studies

A total of 33 STUD/CS including 612 patients were published. The average of the mean/median of follow-up periods was 61.4 (range, 13–107.3) months (28 RPD). Crude survival for OS was 57.1%–66.7% (3 RPD), DSS was 50%–100% (15 RPD), and DFS was 30%–100% (25 RPD). The actuarial 5-year survival rates (11 RPD) were 60%–95.2% for OS (54, 62, 64, 65, 72, 79, 84), 77%–82.6% for DSS (54, 62), 28.6%–86.5% for DFS (18, 58, 64, 65, 71), and 49%–64.2% for RFS (62, 84). The 5-year local control rate was 100% (79), and 10-year survival rates were 42%–93% for OS (54, 65, 72, 84), 53% for DSS (54), and 57.1% for DFS (65). One study reported a 15-year DFS rate of 82.6% (58). Advanced tumors were treated in 0%–100% of patients and were present in $>50\%$ of cases in 90.9% (28/31) of STUD/CS. With Hyams grading (8 RPD), high-grade tumors were noted in 20%–66.7%. NMs and CoRs were achieved in 14.3%–100% each (13 and 15 RPD). Postoperative complications occurred with a frequency of 0%–62.5% (19 RPD). RT was administered in 0%–100% of cases (31 RPD), with a dosage range of 18–90 Gy (19 RPD). ChT was administered in 0%–100% of all cases (31 RPD). Primary tumor progression was observed in three STUD/CS (12.5%–16.7% of

TABLE 1A Summary of results: average of the mean of the parameters investigated in studies/case series and stratified relative to OpS ± E-ass (BCR/TCR ± E-ass; CFR ± E-ass; TFR ± E-ass).

Parameter	Surgical group				
	BCR/TCR ± E-ass (n=7)	CFR ± E-ass (n=33)	TFR ± E-ass (n=10)	OpS ± E-ass total (n=50)	ES (n=44)
Average of follow-up periods (months, mean, median, range) ⁺	53.81 (M 62.3; R 22–84)	61.38 (M 58.5, R 13–107.3)	76.57 (M 75.8; R 33.5–118.5)	63.28 (M 63.7; R 13–118.5)	51.81 (M 44.85, R 12.5–125.2)
Total range of reported follow-up times (months) ⁺	1.3–252	0.1–360	2–225	0.1–360	3–242
Crude survival-OS ⁺ (%, mean, median, range)	94.6 (M 95.4, R 87.5–100)	60.3 (M 57.1; R 57.1–66.7)	62.8 (M 62.8; R 33.3–92.3)	76.1 (M 87.5, R 33.3–100)	98.1 (M 100, R 60–100)
Crude survival-DSS ⁺ (%, mean, median, range)	86.2 (M 90.9; R 66.7–100)	73.1 (M 71.4, R 50–100)	82.3 (M 84.6, R 60–100)	77.4 (M 72.4, R 50–100)	100 (M 100, R 100–100)
Crude survival-DFS ⁺ (%, mean, median, range)	81.5 (M 75, R 73.3–100)	66.9 (M 66, R 30–100)	73.7 (M 76.9, R 33.3–100)	70.4 (M 73.3, R 30–100)	96.5 (M 100, R 76.9–100)
Advanced tumors (%, mean, median, range) ⁺	58.9 (M 53.3, R 13.3–100)	72.0 (M 72.7, R 0–100)	31.4 (M 22.5, R 0–66.7)	61.6 (M 66.7, R 0–100)	37.2 (M 33.3, R 0–100)
Hyams high-grade tumors (% cases/study or case series, mean, range) ⁺	54.9 (M 66.7, R 14.3–86.7)	39.1 (M 36.6, R 20–66.7)	17.7 (M 20, R 0–33.3)	40.1 (M 36.6, R 0–86.7)	27.8 (M 25; R 0–92.6)
Hyams high-grade tumors ≥50% of cases in studies/case series ⁺	60.0	25.0	0	33.3	25.0
Resection status - negative margins (NM) (%, mean, range) ⁺	85.5 (M 85.5; R 71–100) *	71.2 (M 75, R 14.3–100)	71.1 (M 80, R 33.3–100)	72.6 (M 75, R 14.3–100)	88.5 (M 92.3, R 50–100) *
Resection status – gross total resection (GTR; %, mean, range) ⁺	70.3 (M 100, R 11–100) *	69.9 (M 25; R 25–100)	75 (M 75; 50–100)	71.3 (M 92.3; R 11–100)	74.4 (M 100; 7.7–100)*
Complete resection total (NM or GTR/patients total; %, mean, range) ⁺	95.5 (M 100, R 82–100) *	75.7 (M 78.6, R 14.3–100)	84.3 (M 96.1, R 33.3–100)	80.9 (M 84.6, R 14.3–100)	89.0 (M 100, R 50–100) *
Postoperative complications (%, mean, range) ⁺	25.0 (M 30, R 0–42.3)	19.5 (M 16.7, R 0–62.5)	12.6 (M 7.7, R 0–40)	19.4 (M 18.4, R 0–62.5)	10.5 (M 5.7, R 0–60)
Pre-/postoperative RT (%, mean, range) ⁺	81.6 (M 80.0, R 40–100)	76.8 (M 81.3, R 0–100)	69.1 (M 75, R 0–100)	76.0 (M 80.0, R 0–100)	83.8 (M 90.3, R 0–100)
Pre-/postoperative ChT (%, mean, range) ⁺	10.6 (M 6.7, R 0–33.3)	32.0 (M 23.1, R 0–100)	10.7 (M 3.9, R 0–33.3)	24.7 (M 16.7, R 0–100)	18.9 (M 0, R 0–88.9)
First recurrences (%, mean, range) ⁺	33.8 (M 28.6, R 0–66.7)	35.1 (M 33.3, R 0–83.3)	23.4 (M 15.4, R 0–61.5)	32.6 (M 33.3, R 0–83.3)	14.8 (M 10, R 0–100%)
Time to first recurrences (range, months) ⁺	1–78 [#]	1–312	2–84	1–312	3–168
Primary tumor progression (%)	6.7%	14.9 (12.5–16.7)	0/7.7 ~	12.8 (6.7–16.7)	0

⁺If available: not in all studies reported; *71% NM and 11% GTR summarize to an 82% complete resection rate in one and 7.7% and 92.3% in another publication; [#]a mean of 82.1 months reported in the study of Ward et al. (34); ~one case after TFR (7.7%) out of a case series (21).
BCR, bicoronal resection; CFR, craniofacial resection; ChT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; E-ass, endoscopy-assisted; ES, endoscopic surgery; GTR, gross total resection; NM, negative margins; OpS, open surgery OS, overall survival; RT, radiotherapy; TCR, transcranial resection; TFR, transfacial resection.

TABLE 1B Summary of results: average of the mean of the parameters investigated in single cases in case series/case reports, and stratified relative to OpS ± E-ass (BCR/TCR ± E-ass; CFR ± E-ass; TFR ± E-ass; total) and endoscopic surgery (ES).

Parameter	Surgical group				
	BCR/TCR ± E-ass (n=11)	CFR ± E-ass (n=16)	TFR ± E-ass (n=11)	OpS ± E-ass total (n=38)	ES (n=40)
Follow-up period (months, mean, median, range) ⁺	35.73 (M 14.0, R 6–102)	33.31 (M 16, R 3–134)	21.6 (M 21.5, R 10–36)	30.86 (M 18, R 3–134)	32.11 (M 24, R 3–120)
Crude survival (%) ⁺ -OS	100	87.5	81.8	89.5	97.5
Crude survival (%) ⁺ -DSS	100	87.5	81.8	89.5	97.5
Crude survival (%) ⁺ -DFS	81.8	87.5	63.6	78.9	97.5
Advanced tumors (%) ⁺	90.9	87.5	30.0	73.0	35
Hyams high-grade tumors (%) ⁺	16.7	60.0	42.9	43.5	35.0
Resection status ⁺ -NM (%)	50	33.3	100	40.9	66.7
Resection status ⁺ -GTR (%)	55.5	80	100	91.7	100
Resection status (%) ⁺ - NM or GTR (%)	77.8	53.3	100	69.0	78.1
Postoperative complications (%) ⁺	40.0	21.4	25	28.1	5.6
Pre-/postoperative RT (%) ⁺	90.9	85.7	72.7	83.3	67.5
Pre-/postoperative ChT (%) ⁺	45.5	42.9	9.1	33.3	10.0
First recurrences (%) ⁺	27.3	18.8	36.4	26.3	7.5
Time to first recurrences (months) ⁺	2–29	1–60	12–13	1–60	5–24
Primary tumor progression (%)	0/9.1 ~	6.25	0	2.6/5.3 ~	0

⁺If available; not in all studies reported; ~one case report after TCR/BCR (44).
BCR, bicoronal resection; CFR, craniofacial resection; ChT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; E-ass, endoscopy-assisted; ES, endoscopic surgery; GTR, gross total resection; NM, negative margins; OpS, open surgery OS, overall survival; RT, radiation therapy; TCR, transcranial resection; TFR, transfacial resection.

cases). First recurrences after surgery were observed in 9.1%–83.3% of the cases (30 RPD) after time intervals ranging from 1 to 312 months (Table 1a; Supplementary Table S2).

3.2.2 Single cases/case reports

Two single cases were described in STUD/CS (74, 76), while CRs described 14 cases (52, 56, 57, 67, 69, 70, 73, 78, 80–83, 86, 87). The mean follow-up period was 33.3 (range, 3–134) months, and the mean OS/DSS/DFS rate was 87.5% each. Kadish stage C lesions were found in 87.5% of all cases and high-grade tumors in 60% (10 RPD). NMs were reported in 33.3 (12 RPD) and CoR in 53.3% (15 RPD). Postoperative complications were noted in 21.4% of all cases. RT was performed in 85.7% and ChT in 42.9% of patients (14 RPD each). First recurrences were observed in three cases. Tumor progression occurred in one case (67). Another patient had a recurrence and signs of an unfavorable tumor (Kadish stage C, high grade, and positive margins) (74). Both patients died (Table 1b; Supplementary Table S2).

3.3 TFR ± E-ass

A total of 21 STUD/CS including 82 patients were published from 1992 to 2018. Results after TFR-E-ass were published in 12 STUD/CS (21, 47, 48, 59, 60, 68, 72, 88–92) and results after TFR +E-ass in nine (66, 74, 93–99).

3.3.1 Case series/studies

A total of 10 STUD/CS were published including 71 patients with results after TFR ± E-ass (21, 47, 48, 60, 66, 68, 72, 88, 94, 95). The average of the mean follow-up times was 76.6 (range, 33.5–118.5) months (8 RPD). Crude survival (maximum of 9 RPD) was 33.3%–92.3% for OS, 60%–100% for DSS, and 33.3%–100% for DFS. Advanced-stage tumors were present in >50% of the patients in three STUD/CS (10 RPD). Hyams high-grade tumors were present in 0%–33.3% (3 RPD). NMs and CoR were achieved in 33.3%–100% each (5 and 6 RPD). Postoperative complications were reported in 0%–40% of cases (6 RPD). RT was administered in 80%

of STUD/CS in 53.8%–100% of cases (9 RPD). The dosage and/or range administered (50–65 Gy) were reported in four STUD/CS. ChT was administered in 0%–33.3% of the patients (10 RPD). Primary tumor progression could be suggested in one case after recurrence occurred after a short period in connection with “dead of disease” (DOD) status (7.7%) (21). First recurrences were described in 0%–61.5% of cases after periods ranging from 2 to 84 months (9 RPD, Table 1a; Supplementary Table S3).

3.3.2 Single cases/case reports

Results after TFR ± E-ass were reported in two STUD/CS in one case each (59, 74) and in nine CRs (89–93, 96–99). The average follow-up was 21.6 (range, 10–36) months (10 RPD). The crude survival rates (maximum of 11 RPD) were 81.8% for OS and DSS and 63.6% for DFS. Advanced tumors were present in 30% (10 RPD) and high-grade tumors in 42.9% (7 RPD). NMs and CoR were achieved in all cases reported (3 and 5 RPD). A postoperative complication was noted in 25% (8 RPD). RT was administered in eight cases (11 RPD), and the dosage was described in four cases (all 60 Gy). One patient declined RT and died (93). One patient received ChT. No tumor progression was noted. First recurrences were observed in 36.4% of all cases after a period of 12–13 months (11 RPD, Table 1b; Supplementary Table S3).

3.4 Various OpS ± E-ass

A range of combined and/or staged surgery (same case) or mixed OpS ± E-ass were described in two STUD/CS and three CRs including 44 patients but were not intensely evaluated in this review, as the data were not stratified to the surgical approach (Supplementary Table S4) (100–104).

3.5 Endoscopic surgery

A total of 84 STUD/CS or CRs including 584 patients, published from 2000 to 2023, were selected (2, 14, 18, 28, 29, 32, 36, 38, 45, 59, 61, 63, 65, 66, 68, 71, 74, 75, 77, 85, 105–167). Results after OpS ± E-ass and ES were described in 20 publications (2, 14, 18, 28, 29, 32, 36, 38, 45, 59, 61, 63, 65, 66, 68, 71, 74, 75, 77, 160).

A total of 44 STUD/CS including 544 patients with results after ES were published (2, 14, 18, 28, 29, 32, 36, 38, 45, 61, 65, 66, 68, 71, 74–76, 85, 106, 111, 113, 115, 116, 118, 119, 123, 124, 127, 129, 133, 135–137, 140, 141, 143–145, 149, 152, 153, 155, 157, 160).

The average of the mean follow-up times was 51.8 (range, 12.5–125.2) months (40 RPD). Crude survival rates (maximum of 27 RPD) were 60%–100% for OS, 76.9%–100% for DFS, and 100% for DSS. The actuarial 5-year survival was 84.6%–100% for OS (65, 119, 133, 137, 152, 153, 155, 160), 100% for DSS (129, 155), 50%–100% for DFS (18, 65, 71, 74, 75, 129, 133, 137, 152, 153, 160), 75%–92.9% for RFS (133, 155), and 38.5% for PFS (85). The 10-year survival was 87.5%–100% for OS (65, 85, 137) and 75.6% and 90% for DFS (65, 137).

3.5.1 Case series/studies

Advanced stage tumors were present in 0%–100% (41 RPD), and in 47.7% of the STUD/CS, ≥50% of the patients treated had advanced tumor stages. High-grade tumors were present in 0%–92.6% of cases (21 RPD). NMs (27 RPD) and CoR (31 RPD) were achieved in 50%–100% of cases each. Interestingly, conversion from ES to OpS ± E-ass was described only in publications in individual cases up to the year 2010 (32, 111, 113, 123) but was no longer reported later. Postoperative complications occurred in 0%–60% (28 RPD). RT was performed in 41 STUD/CS in 33.3%–100% of the patients (42 RPD). The dosage range was 24–66Gy (21 RPD). ChT was administered in 22 studies in 7.7%–88.9% (42 RPD). Primary tumor progression was not observed. First recurrences (40 RPD) were reported to occur with a mean rate of 14.8% per STUD/CS (range, 0%–100%) and after time intervals of 3–168 months (16 RPD) (Table 1a; Supplementary Table 5A).

3.5.2 Single cases/case reports

Results after treatment of only one case (SC/CR) with ES were reported in 40 publications. In three of these, ES was part of STUD/CS that also included OpS ± E-ass (59, 63, 77), and 37 were CRs in which specific situations (e.g., sense of smell preservation and specific histopathology), treatment of advanced tumors, tumors with an atypical/ectopic location, or tumors presenting with unusual symptoms were addressed (105, 107–110, 112, 114, 117, 120–122, 125, 126, 128, 130–132, 134, 138, 139, 142, 146–148, 150, 151, 154, 156, 158, 159, 161–167).

The mean follow-up period was 32.1 (range, 3–120) months. The crude data for OS/DSS/DFS showed 97.5% each. Kadish stages C/D were noted in 35% of the lesions, and Hyams grade III/IV tumors were present in 35.7% (20 RPD). NMs were achieved in 66.7% and CoR in 78.1% of cases (24 and 32 RPD). Postoperative complications were reported in 5.6% (36 RPD). RT was administered in 67.5% of all patients and ChT in 10%. No tumor progression was noted, but first recurrences were observed in 7.5% after 5–24 months. The only patient who died had a Kadish-C, high-grade ENB with a distant recurrence after 5 months (130) (Table 1b; Supplementary Table S5B).

3.6 Comparison of OpS ± E-ass and ES

The results of this review, classified relative to STUD/CS and SC/CR and comparing OpS ± E-ass (BCR/TCR ± E-ass, CFR ± E-ass, and TFR ± E-ass) and ES, are summarized in Tables 1a, b and 2a, b.

3.6.1 Studies/case series

In comparison with OpS ± E-ass, the mean follow-up period was significantly shorter after ES ($p=0.048$), mainly due to the longer time after TFR ± E-ass ($p=0.034$). Crude OS, DSS, and DFS rates were significantly higher after ES in comparison with OpS ± E-ass (all $p=0.0001$), CFR ± E-ass (DSS and DFS, $p=0.0001$ each), and TFR ± E-ass (DFS, $p=0.047$). Actuarial survival rates relative to the surgical approach were not identified in STUD/CS on BCR/TCR ± E-ass and

TABLE 2a Statistics for the parameters investigated in studies/case series: comparison of mean values for parameters in OpS $\pm$ E-ass (BCR/TCR $\pm$ E-ass, CFR $\pm$ E-ass, and TFR $\pm$ E-ass) and endoscopic surgery (ES).

Compare of OpS stratified to various types of OpS with ES and of all types of OpS with ES	BCR/TCR $\pm$ E-ass vs. ES	CFR $\pm$ E-ass vs. ES	TFR $\pm$ E-ass vs. ES	OpS $\pm$ E-ass vs. ES
Studies/case series				
Average for mean follow-up period/study [#]	n.s. ($P = 0.715$)	n.s. ($P = 0.116$)	$p = 0.034$	$p = 0.048$
OS rates/study ^{# ~}	n.n. ⁺	n.n. ⁺	n.n. ⁺	$p = 0.0001$
NED/DFS rates/study ^{# ~}	$p = 0.013$	$p = 0.0001$	$p = 0.047$	$p = 0.0001$
DSS rates/study ^{# ~}	$p = 0.035$	$p = 0.0001$	n.n. ⁺	$p = 0.0001$
Frequency of advanced tumors/study [#]	n.s. ($p = 0.131$)	$p = 0.0001$	n.s. ($p = 0.658$)	$p = 0.0001$
Studies with advanced tumors: $\geq 50\%$ of all cases (yes vs. no) [*]	n.s. ($p = 0.419$)	$p = 0.0001$	n.s. ($p = 0.483$)	$p = 0.006$
Hyams grading III–IV frequency/study	n.s. ($p = 0.057$)	n.s. ($p = 0.153$)	n.n. ⁺	n.s. ($p = 0.064$)
Hyams grading III–IV: $\geq 50\%$ of all cases (yes vs. no) [*]	n.s. ($p = 0.287$)	n.s. ($p = 1.0$)	n.n. ⁺	n.s. ($p = 0.397$)
Negative margins rate/study [#]	n.n. ⁺	$p = 0.008$	n.s. ($p = 0.201$)	$p = 0.009$
Complete resection rate/study (NM or GTR) [#]	n.n. ⁺	$p = 0.036$	n.s. ($p = 0.715$)	n.s. ($p = 0.234$)
Surgical complication rates/study [#]	$p = 0.022$	$p = 0.046$	n.s. ($p = 0.809$)	$p = 0.022$
Surgical complication (yes vs. no) [*]	n.s. ($p = 0.203$)	n.s. ($p = 0.226$)	n.s. ($p = 1.0$)	n.s. ($p = 183$)
RT % of patients/study [#]	n.s. ($p = 0.769$)	n.s. ($p = 0.065$)	n.s. ($p = 0.091$)	$p = 0.043$
RT (yes vs. no) [*]	n.s. ($p = 1.0$)	n.s. ($p = 1.0$)	n.s. ($p = 0.313$)	n.s. ($p = 1.0$)
ChT % of patients/study [#]	n.s. ($p = 0.964$)	$p = 0.041$	n.s. ($p = 0.689$)	n.s. ($p = 0.175$)
ChT (yes vs. no) [*]	n.s. ($p = 0.671$)	$p = 0.029$	n.s. ($p = 1.0$)	n.s. ($p = 0.084$)
Recurrence % of patients/study [#]	$p = 0.036$	$p = 0.0001$	n.s. ($p = 0.468$)	$p = 0.0001$
Recurrence (yes vs. no) [*]	n.s. ($p = 0.215$)	$p = 0.020$	n.s. ($p = 1.0$)	$p = 0.037$

[#]Mann–Whitney *U*-test/Fisher's exact test; ^{*}chi-square exact test; ⁺no statistics: too few cases per group; [~]Values were calculated from (raw) material in reports with variable follow-up times. BCR, bicoronal transection; CFR, craniofacial resection; ChT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; ES, endoscopic surgery; NED, no evidence of disease; OpS, open surgery; OS, overall survival; RT, radiation therapy; TCR, transcranial resection; TFR, transfacial resection. Bold letters/values should highlight significant results.

TABLE 2b Statistics for the parameters investigated in single cases in case series/case reports: comparison of mean values for parameters in OpS $\pm$ E-ass (BCR/TCR $\pm$ E-ass, CFR $\pm$ E-ass, and TFR $\pm$ E-ass) and endoscopic surgery (ES).

Compare of OpS stratified to various types of OpS with ES and of all types of OpS with ES	BCR/TCR $\pm$ E-ass vs. ES	CFR $\pm$ E-ass vs. ES	TFR $\pm$ E-ass vs. ES	OpS $\pm$ E-ass vs. ES
Single cases in case series/case reports				
Average of mean follow-up [#]	n.s. ($p = 0.580$)	n.s. ($p = 0.246$)	n.s. ($p = 0.873$)	n.s. ($p = 0.195$)
OS, yes or no ^{*~}	n.s. ($p = 1.0$)	n.s. ($p = 0.193$)	n.s. ($p = 0.114$)	n.s. ($p = 0.195$)
DSS, yes or no ^{*~}	n.s. ($p = 1.0$)	n.s. ($p = 0.193$)	n.s. ($p = 0.339$)	n.s. ($p = 0.195$)
NED/DFS, yes or no ^{*~}	n.s. ($p = 0.114$)	n.s. ($p = 0.193$)	$P = 0.006$	$p = 0.013$
Advanced tumors, yes vs. no [*]	$p = 0.001$	$p = 0.0001$	n.s. ($p = 1.0$)	$p = 0.001$
Hyams grading III–IV, yes vs. no [*]	n.s. ($p = 0.628$)	n.s. ($p = 0.255$)	n.s. ($p = 1.0$)	n.s. ($p = 0.756$)
Negative margins rate, yes vs. no [*]	n.s. ($p = 1.0$)	$p = 0.022$	n.s. ($p = 0.532$)	n.s. ($p = 1.0$)
Complete resection rate (NM or GTR) [*]	n.s. ($p = 0.601$)	n.s. ($p = 0.10$)	n.s. ($p = 0.560$)	n.s. ($p = 0.562$)
Surgical complications, yes vs. no [*]	$p = 0.015$	n.s. ($p = 0.126$)	n.s. ($p = 0.145$)	$p = 0.019$
RT, yes vs. no [*]	n.s. ($p = 0.153$)	n.s. ($p = 0.302$)	n.s. ($p = 1.0$)	n.s. ($p = 0.184$)

(Continued)

TABLE 2b Continued

Compare of OpS stratified to various types of OpS with ES and of all types of OpS with ES	BCR/TCR ± E-ass vs. ES	CFR ± E-ass vs. ES	TFR ± E-ass vs. ES	OpS ± E-ass vs. ES
Single cases in case series/case reports				
ChT, yes vs. no *	<i>p</i> = 0.015	<i>P</i> = 0.013	n.s. (<i>p</i> = 1.0)	<i>p</i> = 0.022
Recurrence, yes vs. no *	n.s. (<i>p</i> = 0.106)	n.s. (<i>p</i> = 0.338)	<i>p</i> = 0.031	<i>p</i> = 0.034

*Mann-Whitney U-test/Fisher's exact test; *Chi-square exact test; *no statistics: too few cases per group. ~ Values were calculated from (raw) material in reports with variable follow-up times. BCR, bicoronal transection; CFR, craniofacial resection; ChT, chemotherapy; DFS, disease-free survival; DSS, disease-specific survival; ES, endoscopic surgery; NED, no evidence of disease; OpS, open surgery; OS, overall survival; RT, radiation therapy; TCR, transcranial resection; TFR, transfacial resection. Bold letters/values should highlight significant results.

TFR ± E-ass but were available for CFR ± E-ass and ES. For CFR ± E-ass, the actuarial 5-year OS was 60%–95.2%; for 5-year DSS, 77–82.6%; for 5-year DFS, 28.6%–86.5%; and for 5-year RFS, 49%–64.2%. In comparison, the actuarial survival after ES was higher, at 84.6%–100% for 5-year OS, 100% in the average for 5-year DSS, 50%–100% for 5-year DFS, and 75%–92.9% for 5-year RFS. After CFR ± E-ass, the 10-year survival rates were 42%–93% for OS, 53% for DSS, and 57.1% for DFS. The 15-year DFS reported in one publication was 82.6% (58). In comparison, after ES, the actuarial 10-year OS was 87.5%–100% and the 10-year DFS was 75.6%–90%.

Significantly more advance-stage tumors were treated with OpS ± E-ass, mainly due to the significantly larger number treated by CFR ± E-ass (*p*=0.0001 each). With regard to Hyams grade III–IV tumors, there was a tendency toward a higher frequency in ES in comparison with BCR/TCR ± E-ass and OpS ± E-ass cases, but no significant differences. After ES, higher rates of NMs were observed in comparison with OpS ± E-ass (*p*=0.009), and higher rates of NMs and CoRs were described compared to CFR ± E-ass (*p*=0.008 and *p*=0.036). Compared to BCR/TCR, CFR ± E-ass, and OpS ± E-ass, significantly lower rates of postoperative complications (*p*=0.022, *p*=0.046, and *p*=0.022) and fewer recurrences (*p*=0.036, *p*=0.0001, and *p*=0.0001) were described after ES. In addition, RT was administered after ES significantly less often compared to OpS ± E-ass (*p*=0.043) and ChT compared to CFR ± E-ass (*p*=0.041). In general, the differences were most significant when ES was compared to CFR ± E-ass (Tables 1a, 2a; Figures 2a, 3a).

3.6.2 Single cases/CRs

In comparison with ES, DFS was significantly lower after TFR ± E-ass (*p*=0.006) and OpS ± E-ass (*p*=0.013), and significantly more advanced tumors were treated with BCR/TCR ± E-ass, CFR ± E-ass, or OpS ± E-ass (*p*=0.001, *p*=0.0001, and *p*=0.001). In addition to this, significantly more surgical complications were observed after BCR/TCR ± E-ass and OpS ± E-ass (*p*=0.015, *p*=0.019). Compared to ES, ChT was administered significantly more often after BCR/TCR ± E-ass, CFR ± E-ass, and OpS ± E-ass (*p*=0.015, *p*=0.013, *p*=0.022), and recurrence rates were significantly higher after OpS ± E-ass (*p*=0.034; Tables 1b, 2b; Figures 2b, 3b).

4 Discussion

This review compared the results after OpS ± E-ass, stratified relative to BCR/TCR ± E-ass, CFR ± E-ass, and TFR ± E-ass, and ES for esthesioneuroblastoma selecting 144 reports including 1,434 patients published from 1990 to 2023.

One early meta-analysis evaluated 26 STUD/CS published between 1990 and 2000 including 390 patients after unstratified OpS (12). Average rates of advance-stage tumors (Kadish stage C, 61%; T3–4, 50%) and Hyams grade III–IV tumors (38%), and recurrence rates (29% local, 16% regional, and 17% distant) were reported. Surgery and RT (dosages of 55–65 Gy) were performed in 44%. The average 5-year OS and 5-year DFS were 45% and 41%, respectively, and the 10-year OS was 52%. CFR was the most effective OpS, with a 5-year DFS of 65%. Compared to this, similar results were described in the STUD/CS reporting staged or combined/mixed OpS ± E-ass. Compared with results after CFR ± E-ass found in publications cited in this review, more cases were treated by surgery and RT (76.8%), and better 5-year OS (60%–95.2%) and DFS (28.6%–86.5%) rates and better and 10-year OS (42%–93%) survival rates were described (see Results; Tables 1a, b, 2a, b; Supplementary Tables S1–S4).

ES for esthesioneuroblastoma was investigated in one recent review that included 44 STUD/CS and 399 patients. Reduced morbidity after ES ± RT was highlighted as most important advantages. Among the tumors, 48.3% had a modified Kadish stage C/D, and 34% were Hyams grade III–IV. NMs were achieved in 86.9%, and the mean recurrence rate was 10.3%. The reported mean 5-year survival rate was 91.1% (16). The results of the STUD/CS included in that review were comparable with those found in the present one. In the SC/CR, complete resection was achieved less frequently, presumably due to difficult locations. Nevertheless, low postoperative complication rates, low recurrence rates, and excellent survival rates were reported (Tables 1a, b; Supplementary Tables 5A, B).

Several meta-analyses and reviews comparing ES and OpS ± E-ass have been published. Devaiah et al. presented a meta-analysis including 361 patients treated from 1992 to 2008. Survival after ES was significantly better in comparison with OpS (100% vs. approximately 45%) or E-assisted OpS (100% vs. approximately 50%), also after the results had been stratified according to the publication year. OpS ± E-ass, 63%, was performed for Kadish stage C/D tumors, in comparison with 43.6% for ES. The median follow-up periods were similar for ES and OpS ± E-ass (54.5 vs. 51.0 months) (3).

Komotar et al. presented a review including 47 STUD/CS and 453 patients. Kadish stage A/B tumors were treated with ES significantly more often than with OpS ± E-ass. GTR was achieved in 98.1% of the patients in the ES group, in comparison

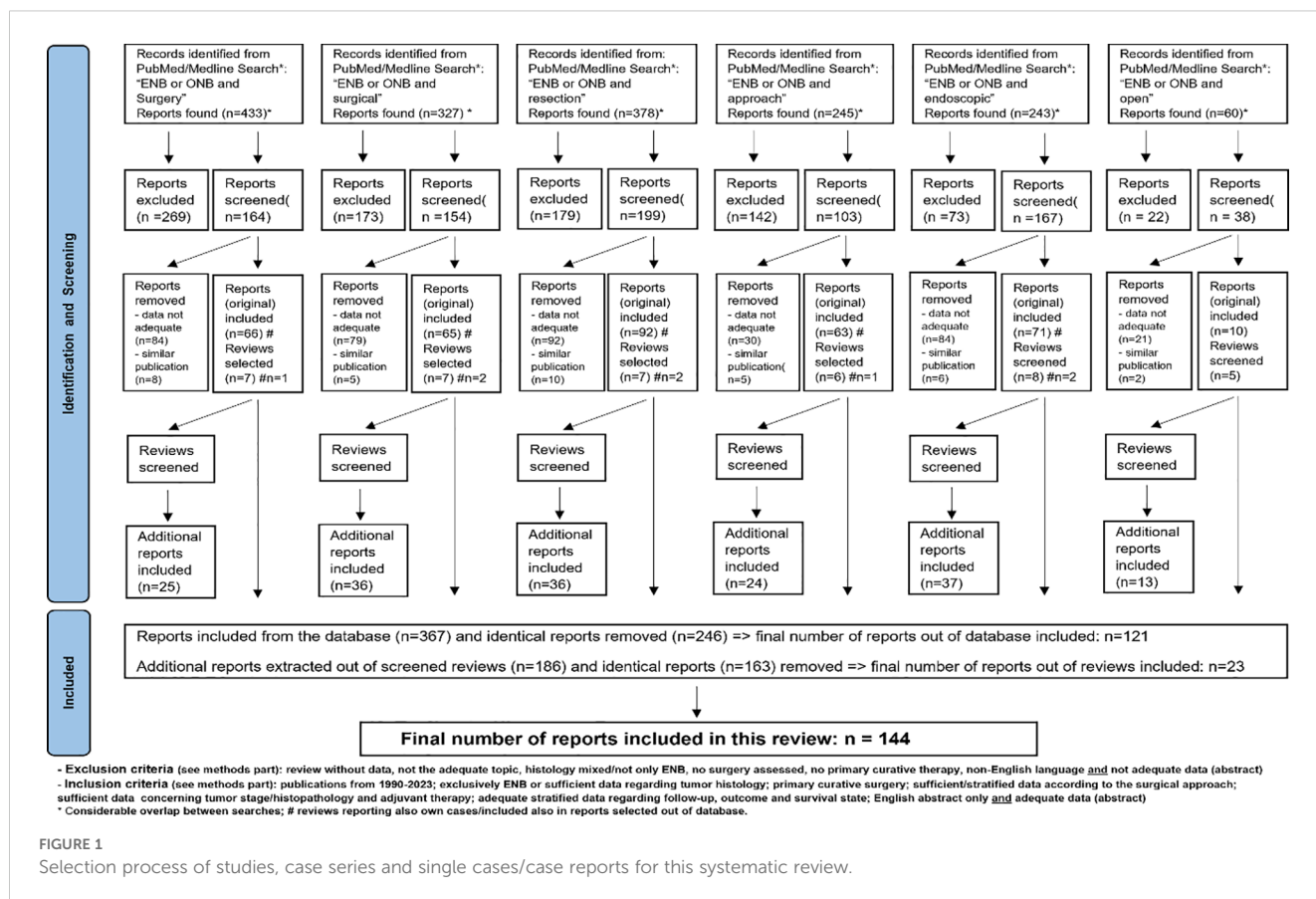


FIGURE 1

Selection process of studies, case series and single cases/case reports for this systematic review.

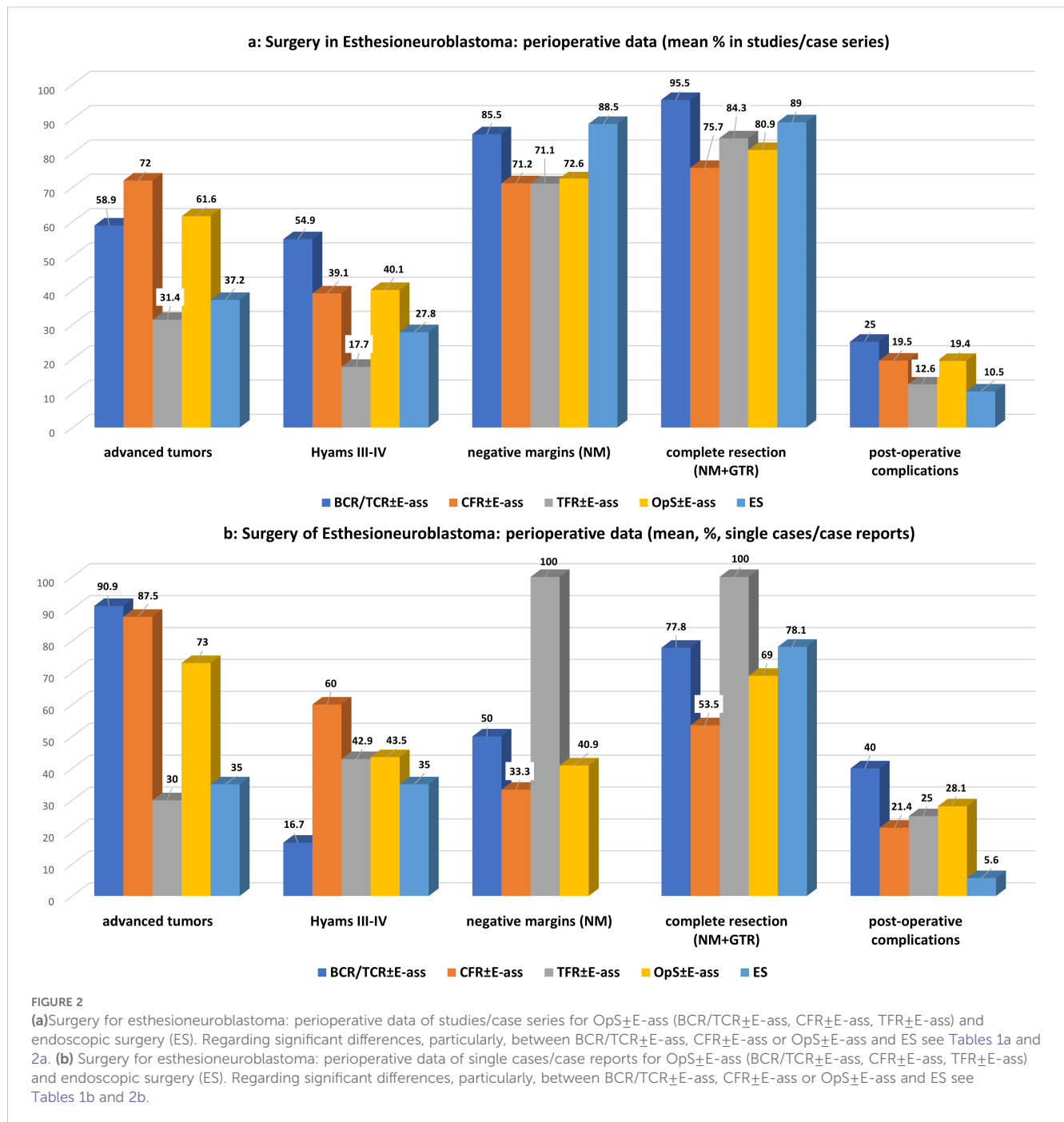
with 81.3% after CFR $\pm$ E-ass and 100% after TCR; NMs were achieved in 93.8% after ES and 95.8% after TCR. The postoperative complication rates were lower after ES. The mean follow-up periods were 71 months after CFR $\pm$ E-ass, 52 months after ES, and 43.1 months after TCR $\pm$ E-ass. Local and regional recurrence rates were lower after ES in comparison with CFR $\pm$ E-ass or TCR $\pm$ E-ass (8.0% vs. 22.1% vs. 16.7%, and 6% vs. 17.3% vs. 8.3%). The 15-year OS and tumor progression-free survival according to Kaplan-Meier analysis were better after ES than after TCR $\pm$ E-ass and CFR $\pm$ E-ass (26).

Fu et al. evaluated 36 STUD/CS including 609 patients. The mean follow-up periods were 67.8 months for OpS $\pm$ E-ass and 52.4 months for ES. After ES, the postoperative complication rates (28.1% vs. 52.9%), frequency of locoregional recurrences (17.4% vs. 45%), distant metastases (1.1% vs. 7.5%), rates of cause-specific (0% vs. 15.2%), and overall mortality (0% vs. 19.9%) were all significantly lower in comparison with OpS $\pm$ E-ass. Although the Kadish stages were also significantly lower, more Hyams grade III-IV tumors were present in the ES group. After OpS $\pm$ E-ass, the median follow-up was 43 (1-312) months. The 5-year OS, DSS, locoregional recurrence-free survival (LRFS), and metastasis-free survival (MFS) rates were 71.2%, 77.5%, 78.8%, and 87.3%, and the 10-y OS, DSS, LRFS, and MFS rates were 57.0%, 72.7%, 61.7%, and 84%. The median follow-up period in the ES group was 32.5 (3-147) months. The 5-year OS, DSS, LRFS, and MFS rates were 100%, 100%, 79.5%, and 89.8%, respectively, and the 10-year OS, DSS, LRFS, and MFS rates were 100%, 100%, 69.6%, and 89.8%, respectively (25).

De Bonnacaze et al. evaluated 24 publications including 283 patients and 15 own patients. After surgery for advance-stage tumors, the highest survival rates were obtained after ES, including over the longer-term course. The 5-year OS rates were 95.8% after ES, 62.5% after OpS+E-ass, and 60.9% after OpS-E-ass (168).

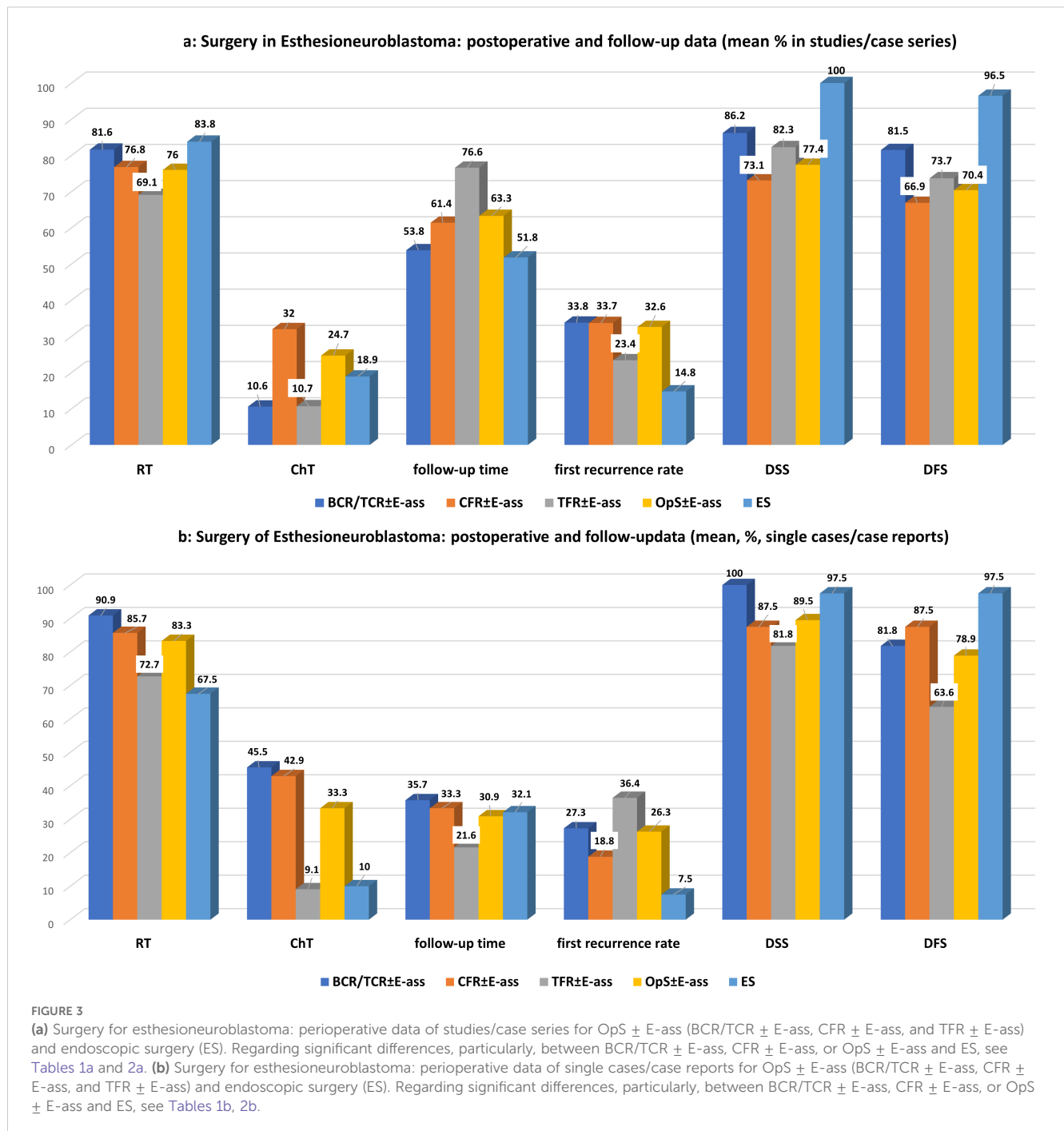
Barinsky et al. reviewed 533 patients from the National Cancer Database; 51.8% underwent OpS $\pm$ E-ass and 48.2% ES. In the ES group, 53.2% of the tumors had Kadish stage C/D stages. After ES, the 5-year OS was 81.9% in comparison with 75.6% after OpS $\pm$ E-ass; a trend toward better survival after ES was observable after multivariate analysis (27).

The present systematic review is the first in which ES was compared to OpS $\pm$ E-ass consistently stratified into BCR/TCR $\pm$ E-ass, CFR $\pm$ E-ass, and TFR $\pm$ E-ass. It similarly showed significant differences between the results with ES and OpS $\pm$ E-ass for nearly all of the parameters tested—more for CFR $\pm$ E-ass than for BCR/TCR $\pm$ E-ass or TFR $\pm$ E-ass, and also more in STUD/CS than in SC/CR. The mean of the average follow-up times was significantly lower after ES in comparison with OpS $\pm$ E-ass (STUD/CS, $p=0.048$), mainly due to the differences compared to TFR $\pm$ E-ass (STUD/CS, $p=0.034$). This is not surprising, as ES was introduced more than 20 years later than all of the OpS $\pm$ E-ass with a measurable shift toward ES recognizable during the last years (Tables 1a, b, 2a, b; Supplementary Tables S1-S5B). The frequency of advanced tumors treated was lower after ES, in particular if compared to OpS $\pm$ E-ass or CFR $\pm$ E-ass cases (STUD/CS, $p=0.0001$ and $p=0.0001$; SC/CR, $p=0.0001$, $p=0.001$) or BCR/TCR $\pm$ E-ass cases (SC/CR, $p=0.001$). Advance-stage tumors



were operated on most often using CFR ± E-ass. Similarly, the proportion of STUD/CS in which >50% advance-stage tumors were present was highest for CFR ± E-ass but lowest and nearly equal for TFR ± E-ass and ES. These data reflect the fact that CFR ± E-ass, as the approach with the greatest invasiveness, is reserved for advance-stage ENBs. Interestingly, if the data were stratified according to the surgical approach, high-grade tumors were not significantly different distributed between ES and all OpS ± E-ass. Hyams grading, although recognized as an important prognostic factor (22, 23, 169–171), was not adequately addressed in many of the publications cited in this review. The available data support the view that its impact on the

choice of surgical approach is limited. The appropriateness of the indication for the adequate surgical approach appears to be more dependent from tumor stage than Hyams grading. Of course, these interrelations should be investigated more intensively in the future ([Tables 1a, b](#); [Supplementary Tables S1–S5B](#)). After ES, rates of NMs were significantly higher compared to CFR ± E-ass (STUD/CS, $p=0.008$) and OpS ± E-ass (STUD/CS, $p=0.009$), rates of total complete resection were significantly higher compared to CFR ± E-ass (STUD/CS, $p=0.036$)—results that also seem to point more toward the lower numbers of advanced tumors than high-grade tumors treated. Nevertheless, the literature also underscores the



advantages of ES for advanced tumors reported in some STUD/CS (14, 26, 27, 65, 116, 118, 123, 129, 144, 160, 172–175). NMs were not achieved in single SC/CR, presumably due to very unusual or difficult locations. The importance of NMs was given greater importance in some reports than the surgical approach selected (14, 25, 27, 65, 174).

Surgical complication rates were significantly higher after BCR/TCR ± E-ass (STUD/CS, $p=0.022$; SC/CR, $p=0.040$), CFR ± E-ass (STUD/CS, $p=0.046$), and all OpS ± E-ass (STUD/CS, $p=0.022$) in comparison with ES, which may indicate that surgery in combination with craniotomy in particular carries a higher risk for postoperative complications. Compared to ES, RT was

applied with significantly lower frequencies compared to all OpS ± E-ass cases (STUD/CS, $p=0.034$), but not compared to the different OpS ± E-ass approaches. ChT was administered significantly more often after CFR ± E-ass (STUD/CS, $p=0.029$; SC/CR, $p=0.013$) and BCR/TCR ± E-ass (SC/CR, $p=0.015$). These data seem to reflect the higher rates of advance-stage tumors and a more complex surgical situation, particularly in cases treated with CFR ± E-ass. Nevertheless, although the rates of NMs were higher, the frequencies of RT/ChT in the ES patients were higher in comparison with OpS ± E-ass cases, possibly because ES was initially regarded as a new technique, and advance tumors were

also resected with it as it emerged. The same causes may be involved in relation to recurrence rates. Rates of recurrences per study were significantly lower after ES in comparison with OpS $\pm$ E-ass (STUD/CS, $p=0.0001$; SC/CR, $p=0.034$), CFR $\pm$ E-ass (STUD/CS, $p=0.0001$), and BCR/TCR $\pm$ E-ass (STUD/CS, $p=0.036$), and in comparison with TFR $\pm$ E-ass (SC/CR, $p=0.031$). Notably, the time ranges after which the first recurrences developed were comparable in all groups. ES showed a favorable outcome in relation to survival rates. In comparison with OpS $\pm$ E-ass, crude OS and DSS (STUD/CS, $p=0.0001$ each), and DFS (STUD/CS, $p=0.0001$; SC/CR, $p=0.013$) were significantly better after ES. When ES was compared with the different OpS $\pm$ E-ass approaches, the most significant differences in DSS or DFS were observed after CFR $\pm$ E-ass (STUD/CS, $p=0.0001$ each) and BCR/TCR $\pm$ E-ass (STUD/CS, $p=0.013$, $p=0.035$). The 10-year actuarial survival reported, available only for ES and CFR $\pm$ E-ass, was higher after ES, at 87.5%–100% for OS and 75.6%–90% for DFS in comparison with 42–93% for OS, 53% for DSS, and 57.1% for DFS after CFR $\pm$ E-ass. In one publication, the 15-year DFS for CFR $\pm$ E-ass was 82.6% (58), with no comparable data for ES. In general, the results were somewhat more favorable in SC/CR, possibly pointing to the fact that cases with specific characteristics and/or a favorable outcome were published. DFS after ES was significantly better compared to OpS $\pm$ E-ass and particularly to TFR $\pm$ E-ass ($p=0.013$, $p=0.006$; Tables 1a, b, 2a, b; Supplementary Tables S1–S5B). The superior data published after ES may reflect the superior visualization provided by the magnification and ankle view of the endoscopes.

Overall, the data obtained in this review show that the results after ES are at least equivalent to OpS $\pm$ E-ass approaches in patients with ENB (Tables 1a, b, 2a, b; Figures 2a, b, 3a, b). ES was introduced 20 years ago, and advanced tumors were initially operated on less often using the technique. It was later reported that ES alone can achieve CoR even for more advanced tumor stages, provided that limitations are recognized and respected (14, 26, 27, 65, 116, 118, 123, 129, 144, 160, 172–175). In one report, the highest survival rates after surgery for advanced tumors were obtained after ES even over a longer-term course, with a 5-year OS of 95.8% (168). In another, it was found that NMs were achieved significantly more often after ES (84.2%) in comparison with OpS $\pm$ E-ass (52.1%) (14). The indication for ES is established mainly depending on the local extent of the tumor, and this is highlighted in most publications addressing ES and in those comparing ES with OpS $\pm$ E-ass (3, 25–27, 65, 168, 174). Growing experience with ES is reflected in the fact that conversion from ES to OpS $\pm$ E-ass was described in single cases up to the year 2010 (32, 111, 113, 123) but not after that (Supplementary Tables 5A, 5B). Extended endoscopic endonasal transtuberulum/transplanum approach (EEA-TTP), as mentioned in the therapy of benign conditions (176), may represent the limit for ENB with cranial extension. As ENB is a malignant tumor, it may be necessary, even after an extended ES has been performed, to supplement it by an open approach with or without endoscopic assistance (craniotomy $\pm$ E-ass) due to difficulties to achieve negative margins and the risk for massive complications caused by tumor infiltration of important/vital anatomical structures.

In this context, it has to be mentioned that new development in the radiation therapy, namely, by the introduction of radio-

enhancers or peptide receptor radionuclide therapy, might influence the surgical decision making in these tumors, in particular in cases in which negative margins are expected to be difficult or not to achieve. Whether a major operative trauma could be avoided by applying a less-invasive surgical procedure, followed by radiation therapy with radio-enhancers or peptide receptor radionuclide therapy, which is sparing surrounding healthy cells, might be one of the most interesting topics for future research (177, 178).

Limitations of the review are the heterogeneity of the studies regarding patient number, design, follow-up time, and the report of prognostic histopathological factors (e.g., Hyams grading, Ki-67), resection state, surgical complications, details of the adjuvant therapy, and recurrence rates. Not all parameters of interest were included in every case series/study or report of single cases.

5 Conclusion

The data presented in this review support the conclusion that ES may be regarded as the surgical method of first choice for ENBs with Kadish stages A–B/T1–2. If limitations are respected, ES may be also a possible alternative in carefully selected advanced ENBs with Kadish stage C/T3 (14, 26, 27, 65, 116, 118, 123, 129, 144, 160, 172–175). BCR/TCR $\pm$ E-ass and CFR $\pm$ E-ass, in particular, are the surgical approaches of choice if the extent of an ENB exceeds the limits in terms of cranial extension (Kadish stage C/T4—e.g., brain, skull base, and optical nerve) and/or caudal extension (orbit and maxillary bone) (2, 31, 58, 179, 180). TFR $\pm$ E-ass is reserved for ENBs that mainly have an increased caudal extension (e.g., orbit, bone of nasal floor, or maxilla) (21, 88, 94, 95). In many cases, it is clear that an adequate surgical treatment, in particular (extended) ES or combined approaches, are associated with the best success rates if an adequate setting/skillset is available and an interdisciplinary team (ENT, neurosurgery, and maxillofacial) is involved.

The clinical implications of findings found in this review for practitioners are that these tumors can be treated successfully by (extended) ES in a substantial part of the cases. In extended tumor growth, open approaches with or without E-ass are indicated. Consequently, such cases should be managed by a multidisciplinary team in high-volume units.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

MK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software,

Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MB: Conceptualization, Formal Analysis, Writing – review & editing, Validation. S-MS: Formal Analysis, Validation, Writing – review & editing. MA: Formal Analysis, Validation, Writing – review & editing. HI: Formal Analysis, Supervision, Validation, Writing – review & editing, Methodology, Resources. SM: Formal Analysis, Supervision, Validation, Writing – review & editing, Conceptualization.

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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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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2025.1512771/full#supplementary-material>

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Supracricoid partial laryngectomy and reconstruction of the anterior epiglottic space flap: a new surgical approach for supracricoid partial laryngectomy

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Objective: To introduce a novel surgical technique for partial laryngectomy involving the reconstruction of the epiglottic space flap (ESFR) on the cricoid cartilage, and to compare its clinical efficacy and functional outcomes with those of cricohyoidoepiglottopexy (CHEP) in the treatment of laryngeal squamous cell carcinoma, exploring the feasibility and clinical significance of this new surgical approach.

Methods: A retrospective analysis was conducted on 57 patients with laryngeal squamous cell carcinoma who were treated between January 2014 and January 2020. The inclusion criteria were suitability for CHEP according to the 2002 UICC criteria and the absence of anterior epiglottic space invasion. Postoperative complications, glottic area status, recurrence, and survival were compared between the CHEP group (n=22) and the ESFR group (n=35).

Results: Follow-up (44-116 months; 94.7% rate) revealed similar 3-year (CHEP: 90.6%; ESFR: 91.5%; P>0.05) and 5-year (CHEP: 83.3%; ESFR: 89.3%; P>0.05) cumulative survival. ESFR significantly reduced extubation time (ESFR: 8 ± 2.5 days; CHEP: 18 ± 3.1 days; P<0.01) and swallowing errors (ESFR: 5.7%; CHEP: 22.7%; P<0.05). No significant differences were observed in pharyngeal fistula, laryngeal stenosis, or recurrence rates (P>0.05).

Conclusion: Compared to CHEP, ESFR technique demonstrates equivalent surgical eligibility criteria and oncological resection margins. However, ESFR uniquely preserves the anatomical integrity of the laryngeal framework, enabling superior postoperative functional outcomes through expedited restoration of phonatory and deglutitive capacities while maintaining long-term laryngeal preservation.

KEYWORDS

laryngeal tumor, supracricoid partial laryngectomy, reconstruction surgery, ESFR, CHEP results follow-up (44-116 months, 94.7% rate) revealed similar 3-year (CHEP: 90.6%, ESFR: 91.5%, P>0.05) and 5-year (CHEP: 83.3%)

1 Introduction

In recent years, the treatment strategy for laryngeal cancer has gradually shifted from total laryngectomy to function-preserving surgeries (such as supracricoid partial laryngectomy, SCPL) and non-surgical treatments (such as radiotherapy). Multiple studies (1–3) have shown that for early-stage laryngeal cancer, the survival rates of radiotherapy and surgery are similar, but function-preserving surgeries have advantages in local control and long-term quality of life. The landmark RTOG 91-11 trial (2) showed that for advanced laryngeal cancer, chemoradiotherapy achieves laryngeal preservation rates similar to total laryngectomy but has higher long-term dysphagia and gastrostomy dependence rates in the chemoradiotherapy group, highlighting the trade-offs between organ preservation and functional morbidity. In contrast, function-preserving surgeries provide robust local control while maintaining laryngeal integrity, especially for T3-T4a lesions where surgical margins can be achieved.

Supracricoid partial laryngectomy (SCPL) is a widely accepted surgical technique applicable to both glottic and supraglottic laryngeal cancers, as well as cases of radiotherapy failure and postoperative laryngeal stenosis. SCPL encompasses two main procedures: cricothyroidopiglotomy (CHEP) and cricothyroidopexy (CHP) (4). While SCPL offers advantages such as a relatively simple surgical procedure and good local control rates, it is associated with a higher incidence of postoperative dysphagia and aspiration, along with prolonged extubation times, leading to patient discomfort (5). The emergence of novel approaches, epiglottic space flap reconstruction (ESFR), addresses these limitations by preserving laryngeal framework integrity and minimizing neurovascular disruption. In patients eligible for ESFR, the epiglottic space can be dissected and inferiorly rotated to create a tissue flap for laryngeal reconstruction. This technique, known as supracricoid partial laryngectomy with ESFR, maintains the normal anatomical position of the larynx. Clinical experience indicates that ESFR significantly reduces the incidence of postoperative dysphagia and aspiration, and shortens extubation time. Since January 2016, our institution has adopted ESFR with satisfactory clinical outcomes. This report presents the clinical data of 35 patients with laryngeal cancer who underwent ESFR, comparing and analyzing them with 22 patients who underwent CHEP.

2 Materials and methods

2.1 Research object

A retrospective analysis was conducted on 57 patients with laryngeal cancer admitted to the Department of Otolaryngology, Head and Neck Surgery at West China Hospital of Sichuan University from January 2016 to January 2022. This study utilized the hospital's electronic medical records (EMR). Patients were identified through a structured search of surgical codes (e.g., ICD-

10 codes for laryngeal cancer: C32.x) and procedural terms (e.g., "CHEP," "ESFR," "partial laryngectomy") within the EMR system.

2.1.1 Inclusion criteria

- Pathologically confirmed laryngeal squamous cell carcinoma;
- Tumor not invading the pre-epiglottic space;
- Meeting the CHEP criteria according to the 2002 UICC standard.

2.1.2 Exclusion criteria

- Distant metastasis (M1);
- Bilateral fixation of the arytenoid cartilages;
- Invasion of the perichondrium of the thyroid cartilage.

The CHEP group comprised 22 patients (21 males, 1 female), with ages ranging from 45 to 73 years (median age: 57 years). Clinical staging was based on the 2002 UICC TNM staging criteria. Among these patients, there were 22 cases of glottic laryngeal cancer, including 2 cases classified as T2N0M0, 6 as T2N1M0, 9 as T3N0M0, and 5 as T3N1M0. The ESFR group included 35 patients (33 males, 2 females), with ages ranging from 46 to 75 years (median age: 61 years). All 35 patients in this group had glottic carcinoma, with the following staging distribution: 5 cases of T2N0M0, 7 cases of T2N1M0, 12 cases of T3N0M0, 10 cases of T3N1M0, and 1 case of T4N1M0.

2.2 Surgical procedure

2.2.1 CHEP surgery

General anesthesia was induced via endotracheal intubation. An arc-shaped incision was made in the anterior neck region, followed by the separation of the anterior cervical muscles. The sternohyoid and thyrohyoid muscles were horizontally transected at the upper edge of the thyroid cartilage, and the sternohyoid muscle along with the bilateral pharyngeal constrictor muscles were subsequently cut. The cricothyroid membrane was horizontally incised, the thyrohyoid membrane was excised, and the laryngeal cavity was entered from a superior approach. Starting from the less affected side of the lesion, an incision was made in front of the arytenoid cartilage, taking care to preserve the vocal process and the cricoarytenoid muscle group. The thyroid cartilage was then split along its midline, allowing the laryngeal cavity to be opened in a book-like fashion, and the severely affected contralateral side was removed. Three absorbable sutures (size 1) were passed through the cricoid cartilage under the mucosa, then through the remaining epiglottic cartilage and the anterior epiglottic space, bypassing the hyoid bone to reach the tongue base muscle, and cricoid cartilage hyoid epiglottic fixation was performed. The pharyngeal cavity was closed, and the incision was reinforced by suturing the anterior

cervical muscle layer. A tracheotomy was performed at the lowest point of the curved incision in the anterior neck.

2.2.2 ESFR surgery

With the patient under general anesthesia and an ascending intubation in place, a curved incision is made in the anterior neck region. The anterior cervical muscles are then separated in the midline, and a thyroid hook is used to retract these muscles laterally, thereby fully exposing the thyroid cartilage. The extent of thyroid cartilage resection in ESFR surgery is carefully determined based on tumor location, identified through preoperative visual inspection and image-guided evaluations, including CT (Figure 1A, B). Intraoperative frozen section pathology is used to ensure adequate oncological resection margins, confirmed postoperatively by histopathology. This approach allows for optimal removal of malignant tissue while preserving sufficient thyroid cartilage for functional reconstruction.

The resection typically involves one-third to one-half of the thyroid cartilage along its lateral and upper aspects from both sides, which differs from classical frontolateral partial laryngectomies. Use an electric knife to cut the thyroid cartilage membrane along the upper edge of the bilateral thyroid cartilage plates, and make an arc-shaped incision until it converges at the cricoid thyroid membrane (Figure 2A, B). One-third to one-half of the thyroid cartilage is resected along its lateral and upper aspects from both sides, which differs from classical frontolateral partial laryngectomies (Figure 3A). The thyroid cartilage is incised along the electric knife's cut line to expose the laryngeal cavity, where the tumor is removed, ensuring surgical safety (Figure 3B). The epiglottis root is clamped, and the fibrous adipose tissue, hyoid epiglottic ligament, lingual epiglottic ligament, and epiglottic lingual mucosa in the anterior epiglottic space are freed from bottom to top. The epiglottis is then released and moved downward, with care taken to maintain the integrity of the mucosa attached to the free edge of the epiglottis

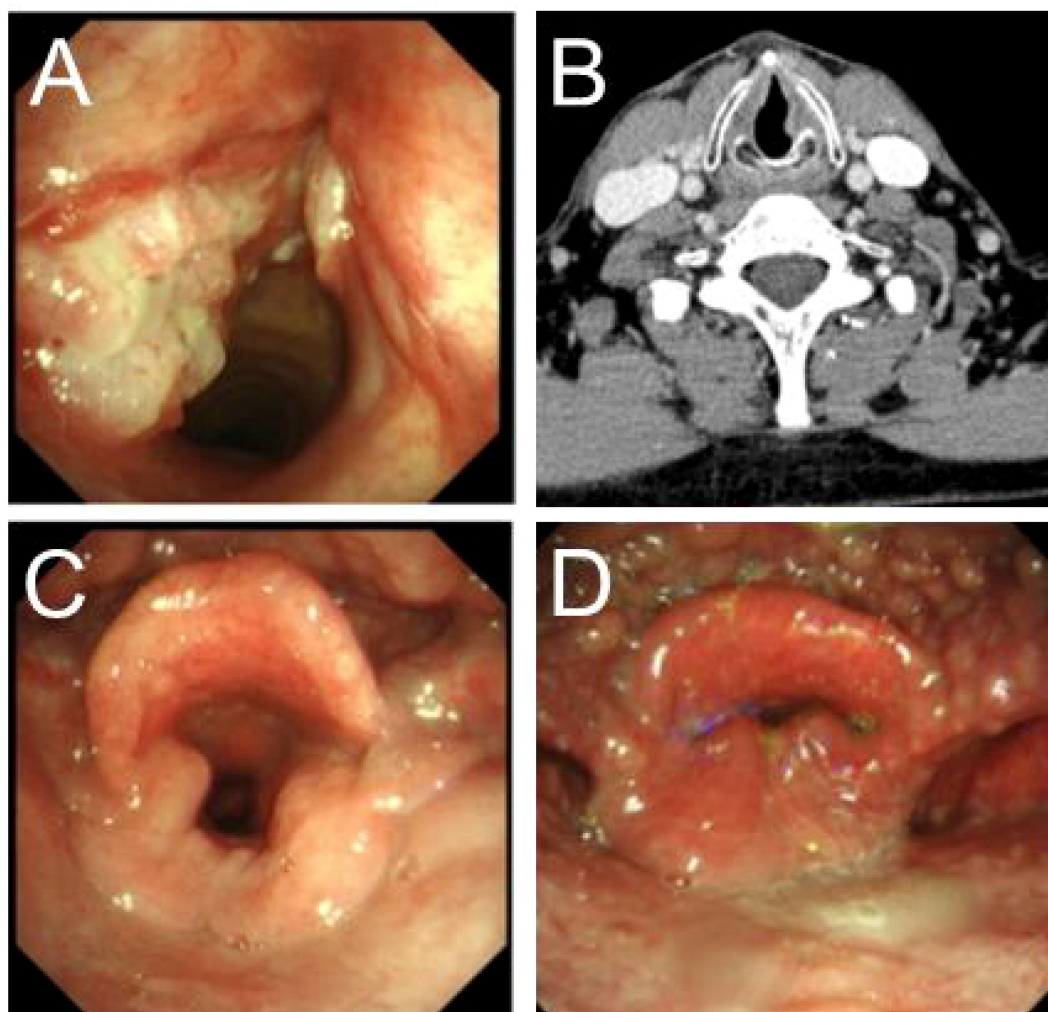


FIGURE 1

Presurgery and postsurgery glottis of patients of supracricoid partial laryngectomy with ESFR surgery. (A) The larynx lesion was examined by preoperative laryngoscopy. (B) Preoperative enhanced CT for laryngeal lesions. (C) Laryngoscopy the opened glottis six months after surgery. (D) Laryngoscopy the closed glottis six months after surgery.

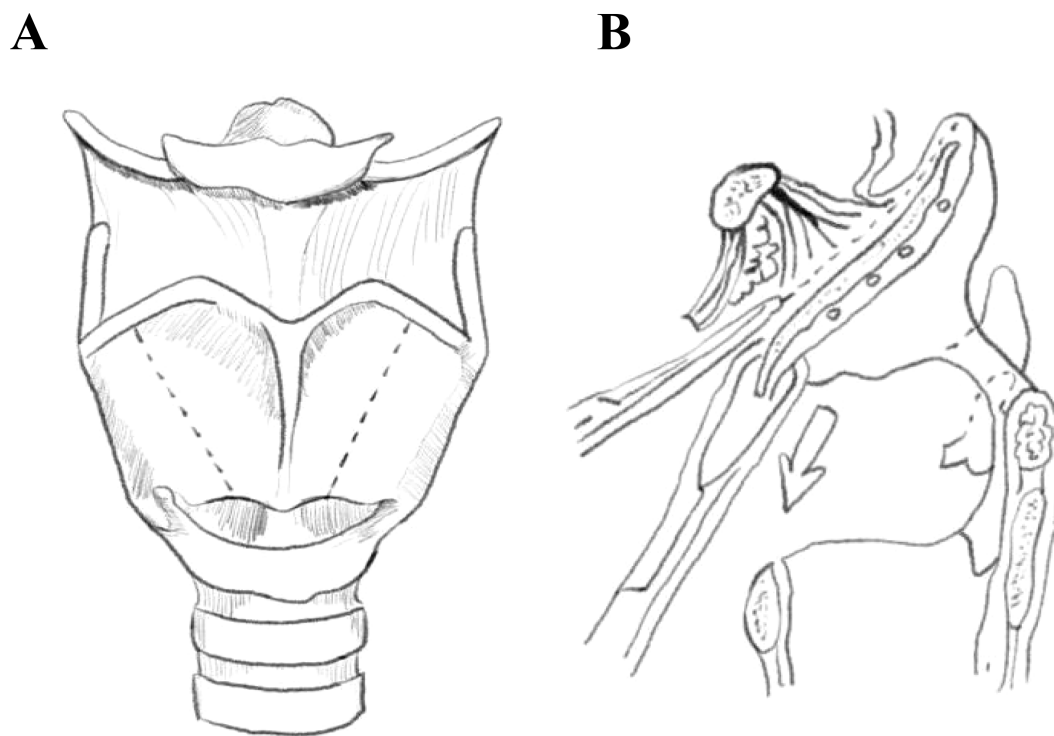


FIGURE 2

Schematic drawing of supracricoid partial laryngectomy with epiglottic space flap reconstruction (ESFR) surgery. (A) The dotted line depicts the region of thyroid cartilage resected during ESFR. (B) The dotted line delineates the intralaryngeal region resected during ESFR.

to ensure blood supply to the epiglottic valve (Figure 3C). The epiglottic valve is pulled down. Three absorbable sutures (size 1) are used to close the glottis flap and cricoid cartilage, sealing the laryngeal cavity. The edge of the epiglottic valve is sutured to the residual thyroid cartilage tissue and the base of the tongue to further seal the laryngeal cavity (Figure 3D). The central part of the epiglottic valve is sutured to the thyroid cartilage to expand the pharyngeal cavity. A drainage tube is placed, the anterior cervical muscle layer is reinforced, the incision is sutured, and a tracheotomy is performed.

2.3 Postoperative outcome analyses

Patients were followed up to evaluate 3-year and 5-year cumulative survival rates. Extubation time and extubation rates were compared between the two groups. The incidence and recurrence rates of complications, including pharyngeal fistula and laryngeal stenosis, were also assessed.

2.4 Statistical analyses

The statistical analysis of survival data for patients with laryngeal cancer was conducted using SPSS 23.0 software. The 3-year and 5-year survival rates were analyzed using the Kaplan-Meier method,

and the differences in survival rates between different surgical procedures were compared using the log-rank test. Multivariate Cox proportional hazards regression was performed to adjust for potential confounders, including age (continuous variable), T-stage (T2 vs. T3), and nodal status (N0 vs. N1). For the comparison of postoperative extubation rates between two groups, the four grid exact test method was used. The comparison of postoperative extubation time between the two groups was conducted using the t-test. To further mitigate selection bias, a *post hoc* propensity score-matched analysis (1:1 matching with caliper = 0.2) was conducted using SPSS 23.0. Matching variables included age (± 5 years), sex, T-stage, and nodal status. Standardized mean differences (SMD) were calculated to assess balance between groups after matching (SMD < 0.1 indicated negligible imbalance).

2.5 Minimizing selection bias

To mitigate potential selection bias, the following measures were implemented:

1. Consecutive enrollment: all patients meeting inclusion criteria during the study periods were consecutively enrolled to avoid selection of favorable cases.
2. Propensity score matching: groups were balanced for age, sex, and T/N-stage using a 1:1 matching algorithm.

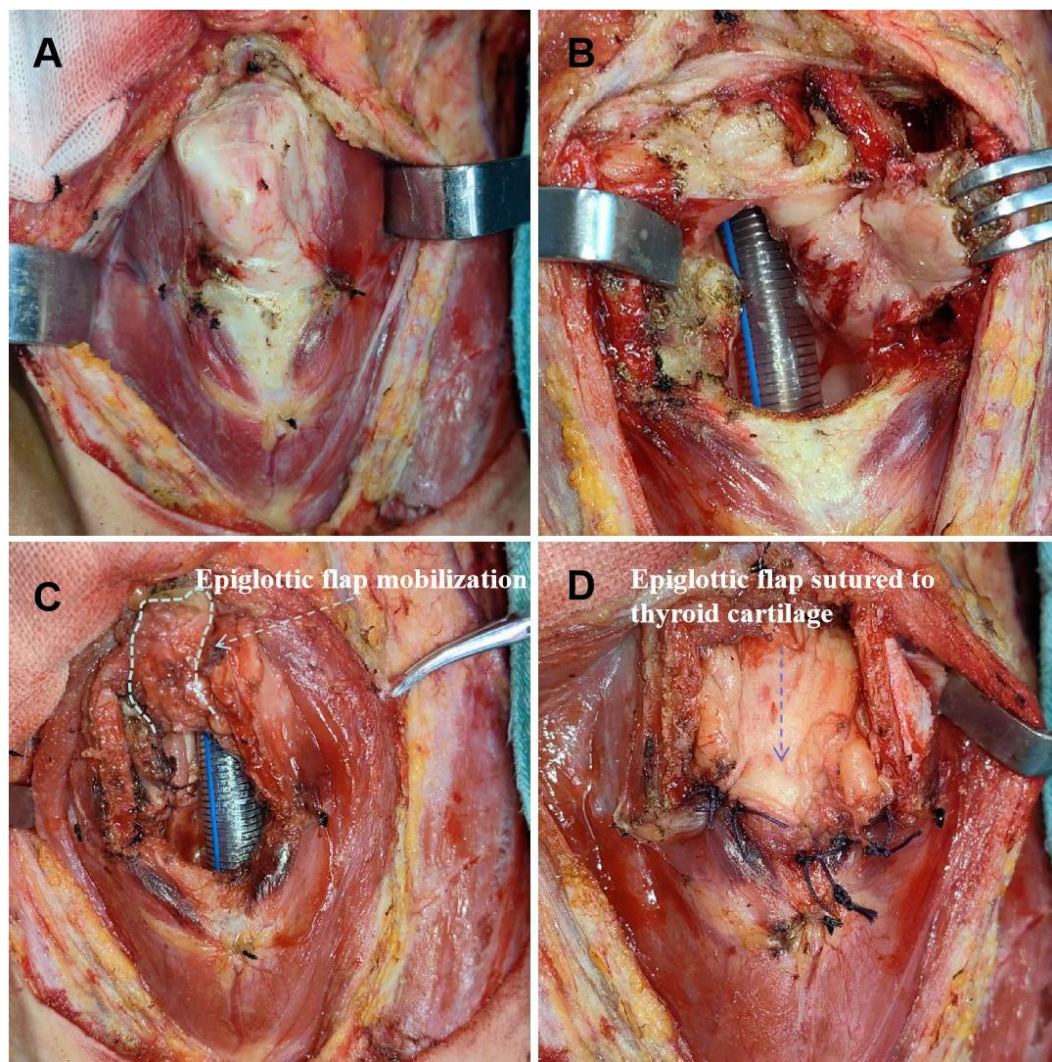


FIGURE 3

Supracricoid partial laryngectomy with ESFR surgical procedure. (A) The thyroid cartilage was cut about 1/3 to 1/2 away from the mediolateral cartilage and removed. (B) The laryngeal cavity was exposed and the lesion was removed. (C) Hold the root of the epiglottis, free the preepiglottic space, release the downward epiglottis. Epiglottic flap mobilization (white dashed line) (D) The epiglottis space flap was closed with the surrounding thyroid cartilage and closed to form a new laryngeal cavity (blue dashed line).

3. Blinded outcome assessment: postoperative complications (e.g., dysphagia, laryngeal stenosis) and survival outcomes were evaluated by clinicians uninvolved in surgical procedures.
4. Multivariate adjustments: Cox regression models adjusted for age, T-stage, and nodal status to control for residual confounding factors.

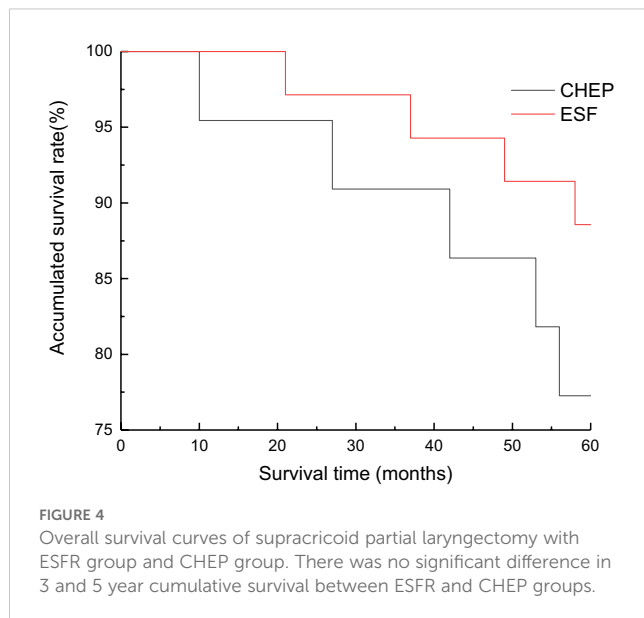
3 Results

3.1 Survival rates

Both the CHEP group (n=22) and the ESFR group (n=35) demonstrated favorable postoperative survival rates. Follow-up data

for the CHEP group revealed that of the 22 patients, all had completed at least 3 years of follow-up, with 2 deaths and 1 loss to follow-up reported. Of the CHEP group, 19 patients had completed 5 years of follow-up, with 3 deaths and 1 loss to follow-up. In the ESFR group, all 35 patients completed at least 3 years of follow-up, with 1 death and 2 losses to follow-up. Of these, 32 patients completed 5 years of follow-up, with 3 deaths and 1 loss to follow-up.

The Kaplan-Meier analysis of the original cohort (n=57) demonstrated comparable 3-year and 5-year survival rates between the CHEP and ESFR groups. Specifically, the 3-year survival rates were 90.6% (95% CI: 85.2–95.0) for the CHEP group and 91.5% (95% CI: 86.7–96.3) for the ESFR group ($P=0.925$). The 5-year survival rates were 83.3% for the CHEP group and 89.3% for the ESFR group ($P=0.873$) (Figure 4). After propensity score matching (n=40, 20 pairs),



the survival outcomes remained consistent. The 3-year survival rates were 89.5% (95% CI: 84.1–94.9%) for the CHEP group and 90.0% (95% CI: 85.0–95.0%) for the ESFR group ($P=0.91$). The 5-year survival rates were 82.4% (95% CI: 75.3–89.5%) for the CHEP group and 87.5% (95% CI: 80.8–94.2%) for the ESFR group ($P=0.72$). Multivariate Cox regression analysis confirmed no significant survival difference between the two groups, with a hazard ratio of 1.12 (95% CI: 0.78–1.61, $P=0.54$), even after adjusting for age and T-staging.

3.2 Extubation time and rate

The postoperative extubation time was 18 ± 3.1 days in the CHEP group and 8 ± 2.5 days in the ESFR group, showing a statistically significant difference ($t=3.50$, $P<0.01$). The postoperative extubation rate was 95.5% (21/22) in the CHEP group and 100% (35/35) in the ESFR group, with no statistically significant difference ($P>0.05$). After 8 weeks of postoperative evaluation, the incidence of swallowing errors was 22.7% (5/22) in the CHEP group and 5.7% (2/35) in the ESFR group. The difference between the two groups was statistically significant ($P<0.05$) as determined by the precision test method.

3.3 Postoperative complications

Both surgical procedures had manageable complications. Pharyngeal fistulas were treated with antiseptic dressings and prophylactic antibiotics, healing within 10–14 days without surgical revision. Patients with fistulas had a median hospital stay of 14 days, compared to 12 days for the CHEP group and 9 days for the ESFR group without complications. No laryngeal stenosis cases were observed, attributed to preserved thyroid cartilage scaffolding in ESFR and early vocal rehabilitation. Standardized protocols, including multidisciplinary reviews and serial videofluoroscopic

swallowing assessments, guided dietary progression and complication mitigation, minimizing reintervention needs and optimizing recovery.

Postoperative pharyngeal fistula occurred in one patient (4.5%) in the CHEP group and one patient (2.9%) in the ESFR group; both cases resolved with wound care. Postoperative recurrence was observed in three patients (13.6%) in the CHEP group and four patients (11.4%) in the ESFR group. No instances of laryngeal stenosis were observed in either group during the follow-up period.

4 Discussion

Recent retrospective analyses, including a 2023 Frontiers study (6), have reinforced the role of surgery in select populations. This multicenter retrospective series of 1,452 patients with T2–T3 laryngeal squamous cell carcinoma reported superior 5-year disease-specific survival rates for surgical cohorts (82% vs. 68% for chemoradiotherapy, $P<0.01$), particularly in tumors with paraglottic or subglottic extension. Compared to radiotherapy, the surgical treatment preserves laryngeal function through anatomical reconstruction and avoids radiation-related complications such as chondronecrosis. For T3–T4a tumors, surgical local control rates may be superior to those achieved with chemoradiotherapy (7).

The fundamental principle of laryngeal cancer surgery involves achieving complete tumor excision while optimizing patient survival, with concurrent prioritization of laryngeal function preservation and postoperative quality of life. The CHEP procedure, originally developed in Europe, represents a significant advancement in functional laryngeal surgery. This technique not only ensures oncological radicality for advanced laryngeal carcinomas but also demonstrates comparable survival outcomes to total laryngectomy while substantially improving quality of life metrics (8). Our institution has undertaken systematic investigation of this surgical approach in recent years. The CHEP cohort exhibited 3-year and 5-year cumulative survival rates of 90.6% and 83.3% respectively, while the ESFR group demonstrated corresponding rates of 91.5% and 89.3%. Consistent with previous reports (9), no statistically significant difference in 3- or 5-year cumulative survival was observed between the two groups.

The rising incidence of laryngeal cancer has spurred the development of varied surgical techniques, with partial laryngectomy representing a substantial proportion (20%–79%) of all laryngeal cancer surgeries (10, 11). Capitalizing on the unique embryological development, anatomical structure, and lymphatic drainage of the larynx, advancements in surgical methods have facilitated the wider adoption of laryngeal function-sparing procedures. These approaches not only improve quality of life but also yield favorable long-term survival outcomes (12). Our department's experience in laryngeal cancer management has evolved from total laryngectomy to partial laryngectomy, incorporating techniques such as CHEP, CHP, and various innovative reconstructive approaches tailored for partial laryngectomy. While these methods preserve laryngeal function and achieve good survival rates, we observed a higher incidence of

postoperative dysphagia and prolonged extubation times with the traditional CHEP procedure. Consequently, since 2014, we have refined the original CHEP technique and adopted the ESFR surgical method, achieving improved clinical results. ESFR preserves laryngeal function by retaining portions of the thyroid cartilage lamina and the epiglottic flap, which maintains the anatomical height of the laryngeal cavity and the configuration of the pyriform sinus, thereby reducing postoperative aspiration (Figure 1C, D). Furthermore, because the cricothyroid joint does not require division, the risk of recurrent laryngeal nerve injury is diminished, promoting early recovery of laryngeal function (13).

At present, both CHEP and ESFR are frequently employed surgical techniques at West China Hospital of Sichuan University. ESFR represents an advancement over CHEP, significantly reducing the incidence of swallowing errors. Given ESFR's capacity to preserve a substantial portion of the thyroid cartilage plates contingent upon the lesion's condition, this study proposes the following optimal indications: ① T2 glottic carcinoma characterized by limited vocal cord mobility and invasion of the laryngeal ventricle; glottic laryngeal cancer with subglottic invasion not exceeding 1 cm. ② T3 glottic carcinoma with invasion of the paraglottic space. Particularly for patients whose tumors involve the contralateral vocal cords but who retain normal function of the contralateral cricoarytenoid joint. In addition to the aforementioned scenarios, traditional CHEP surgery remains a viable option for T4 glottic carcinoma, even when the thyroid cartilage is locally invaded, provided that the outer periosteum remains intact. The selection criteria for ESFR are more stringent than those for traditional CHEP, which has contraindications including glottic tumors with bilateral arytenoid cartilage fixation or invasion of the arytenoid region, extensive subglottic tumor extension, and thyroid cartilage periosteal or extralaryngeal invasion. Consequently, ESFR is generally contraindicated in T4 glottic laryngeal cancers exhibiting more than minimal thyroid cartilage invasion. The advantage of traditional CHEP lies in its broader applicability, whereas ESFR is most appropriately utilized in a carefully defined patient population.

The following considerations are crucial for both surgical techniques: 1. During reconstruction, maintain the anterior inclination of the arytenoid cartilage and ensure that sutures are appropriately tight to preserve its mobility. 2. When repairing the pyriform fossa, employ moderate anterior displacement of the suture line to minimize postoperative swallowing errors. 2. Intraoperatively, take care to protect the recurrent laryngeal nerve to ensure recovery of pyriform fossa function, the reflex mechanisms of the reconstructed larynx, and arytenoid cartilage mobility. At least one cricoarytenoid unit (including the cricoarytenoid muscle group) should be preserved to maintain vocal function in the reconstructed larynx. In ESFR, the central portion of the epiglottic valve is sutured to the thyroid cartilage to expand the pharyngeal cavity and prevent postoperative laryngeal stenosis.

Our findings indicate that ESFR outperforms traditional CHEP significantly in terms of postoperative extubation time and the incidence of swallowing errors at 8 weeks postoperatively. The significantly shorter extubation time observed in the ESFR group (8 vs. 18 days, $P < 0.01$) likely stems from three interrelated

mechanisms: anatomic preservation, reduced neurovascular trauma, and surgical technique-driven airway stability. In ESFR, the retained posterior thyroid cartilage offers structural support for the neoglottis, enabling earlier decannulation. The preserved suprahyoid muscles and intact pyriform fossa anatomy decrease pharyngeal residue and aspiration rates. By maintaining the posterior thyroid lamina and cricoarytenoid units, ESFR prevents laryngeal collapse during swallowing. Avoiding cricothyroid joint dissection reduces superior laryngeal nerve injury, preserving laryngeal sensitivity. The epiglottic flap provides immediate glottic coverage, promoting faster mucosal healing than the exposed cricoid cartilage in CHEP.

We also assessed the severity of postoperative dysphagia and coughing in patients who underwent ESFR. The results revealed that the discomfort associated with these symptoms was significantly less pronounced in ESFR patients compared to those in the traditional CHEP group. This outcome aligns with our clinical expectations and facilitates improved patient recovery. Potential contributing factors include: 1. ESFR's avoidance of upper and lower thyroid cartilage corner resection and cricothyroid joint dislocation, minimizing the risk of recurrent and superior laryngeal nerve injury; Furthermore, the surgical technique is more straightforward, and the intraoperative field of vision is improved. 2. ESFR's preservation of the posterior inferior thyroid cartilage plate may elevate the larynx and trachea during swallowing, and maintain a more normal pyriform sinus configuration. Literature suggests pyriform sinus reduction is the only significant factor in aspiration reduction (14). Since the ESFR procedure maintains a relatively normal anatomical position, the reduction of the pyriform fossa after surgery is faster than with traditional CHEP. Typically, after CHEP surgery, patients who accidentally swallow oral secretions are prone to aspiration. Reduced discomfort, such as choking and coughing, facilitates subsequent swallowing and drinking training, alleviates patient anxiety related to eating, and promotes the development of appropriate swallowing techniques. Earlier occlusion training and vocal exercises can then be implemented to restore laryngeal function (Figure 1C, D). Yüçetürk et al. (13) believe that early extubation promotes timely restoration of phonation and swallowing, mitigates pulmonary infections resulting from aspiration of oral secretions, and consequently reduces both hospitalization duration and the risk of hospital-acquired infections. In summary, the advantages of ESFR include a reduction in the severity of postoperative dysphagia and coughing, leading to accelerated recovery of swallowing function and improved overall patient outcomes.

This study has several limitations. First, the retrospective design introduces potential selection bias. Second, the sample size remains modest, which may limit statistical power. Third, the single-center nature of this study warrants validation through multi-institutional trials. Additionally, the exclusion of tumors involving the preepiglottic space inherently restricts the comparability of ESFR and CHEP. The ESFR technique, although it offers potentially superior functional outcomes in select cases, is inherently limited by its reliance on a healthy epiglottic flap for successful reconstruction. A critical limitation of this approach is the

exclusion of tumors involving the preepiglottic space. This restriction is grounded in sound oncological principles: infiltration of the preepiglottic space typically requires more extensive resection, which compromises the anatomical integrity needed to create a viable epiglottic flap for reconstruction. Thus, while ESFR may significantly enhance functionality for specific patient subsets, as demonstrated in the results, it is not intended to replace existing methodologies but rather to complement them. Finally, the retrospective design and its inherent constraints hinder our capacity to definitively assess the relative benefits and drawbacks of ESFR and CHEP. A prospective, randomized, controlled trial is needed to directly compare these techniques in a carefully selected patient population, stratified by T-stage (T2-T3) and excluding preepiglottic involvement, with standardized postoperative assessments. While this study provides preliminary data on the efficacy of ESFR, a prospective study is essential to definitively evaluate its clinical significance.

5 Conclusion

In conclusion, ESFR emerges as a promising alternative to CHEP for select laryngeal cancer patients, demonstrating superior early functional recovery, as indicated by reduced dysphagia and accelerated extubation, while maintaining comparable long-term survival rates. The success of ESFR is largely attributed to its preservation of key laryngeal structures and reduced risk of nerve damage. However, its application is limited to cases without preepiglottic space involvement, underscoring the importance of stringent patient selection. Although CHEP remains a viable option for more advanced cases, ESFR offers a distinct advantage when anatomical criteria are met. To fully elucidate the clinical significance of ESFR and optimize patient selection, future prospective, randomized trials are essential.

Data availability statement

The datasets presented in this article are not readily available because our raw data are all state secret level data, and papers are reviewed to see if they pose a risk of leakage. Requests to access the datasets should be directed to 15680483625@163.com.

Ethics statement

The studies involving humans were approved by West China Hospital, Sichuan University. The studies were conducted in accordance with the local legislation and institutional

requirements. The 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

CM: Investigation, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Resources, Supervision, Validation. ZH: Conceptualization, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing, Methodology, Project administration. LL: Investigation, Writing – review & editing. YZ: Resources, Writing – review & editing. FC: Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing. XL: Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & 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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