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Article

Transoral Robotic Surgery for Recurrent Tumors of the Upper Aerodigestive Tract (RECUT): An International Cohort Study

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Abstract

Background: Transoral robotic surgery (TORS) is an emerging minimally invasive surgical treatment for residual, recurrent, and new primary head and neck cancers in previously irradiated fields, with limited evidence for its oncological effectiveness. **Methods:** A retrospective observational cohort study of consecutive cases performed in 16 high-volume international centers before August 2018 was conducted (registered at clinicaltrials.gov [NCT04673929] as the RECUT study). Overall survival (OS), disease-free survival, disease-specific survivals (DSS), and local control (LC) were calculated using Kaplan-Meier estimates, with subgroups compared using log-rank tests and Cox proportional hazards modeling for multivariable analysis. Maximally selected rank statistics determined the cut point for closest surgical resection margin based on LC. **Results:** Data for 278 eligible patients were analyzed, with median follow-up of 38.5 months. Two-year and 5-year outcomes were 69.0% and 62.2% for LC, 71.8% and 49.8% for OS, 47.2% and 35.7% for disease-free survival, and 78.7% and 59.1% for disease-specific survivals. The most discriminating margin cut point was 1.0 mm; the 2-year LC was 80.9% above and 54.2% below or equal to 1.0 mm. Increasing age, current smoking, primary tumor classification, and narrow surgical margins (≤1.0 mm) were statistically significantly associated with lower OS. Hemorrhage with return to theater was seen in 8.1% (n = 22 of 272), and 30-day mortality was 1.8% (n = 5 of 272). At 1 year, 10.8% (n = 21 of 195) used tracheostomies, 33.8% (n = 66 of 195) used gastrostomies, and

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66.3% (n = 53 of 80) had maintained or improved normalcy of diet scores. **Conclusions:** Data from international centers show TORS to treat head and neck cancers in previously irradiated fields yields favorable outcomes for LC and survival. Where feasible, TORS should be considered the preferred surgical treatment in the salvage setting.

Despite optimal management, a statistically significant number of patients treated for head and neck cancer (HNC) will experience further disease (1,2). In selected patients, locoregional disease may be treated with curative intent with re-irradiation or surgical excision, where the standard of care is open resection (3-6). Both approaches are associated with morbidity for the patient, but with surgery, much of the tissue disruption relates to the transcervical and/or transmandibular access to the residual or recurrent tumor site, which may be associated with a need for free-flap reconstruction, and not necessarily from the deficit left by removal of the tumor itself (7-9).

Minimally invasive surgical techniques, such as transoral laser microsurgery and transoral robotic surgery (TORS), have emerged in recent decades, seeking to lessen the disruption caused to normal anatomy during tumor resection, seeking to optimize functional outcomes without compromising oncological results (10). Concurrently, the required minimum surgical margin has come under increased scrutiny, with a similar ethos of maximizing the preservation of normal tissues. In salvage cases, the fibrosis related to prior irradiation can collapse the anatomy, bringing tumors into closer proximity to vital structures, thereby limiting the potential resection margin that can be achieved, regardless of the surgical modality used (11).

The interest in moving away from the traditional 5 mm target minimum margin is reflected in the lower values used in contemporary trials employing minimally invasive techniques (12,13). Such trials are not investigating the oncological impact of the reported minimum resection margins following TORS, but rather, they adopt lower margin values as a randomization criterion for adjuvant treatment regimes. It is important to emphasize that all such studies are in the primary disease setting. The optimal minimum margin for tumors arising in previously irradiated fields, either as recurrences or de novo disease, has not yet been defined.

This study aims to report the oncological and functional outcomes in patients undergoing TORS for the treatment of residual, recurrent, and new primary HNC in previously irradiated fields. It also aims to explore the importance of surgical resection margins in this cohort.

Methods

Ethical Considerations and Regulatory Approvals

The protocol was reviewed and approved by the study sponsor (The Royal Marsden NHS Foundation Trust), East of England—Cambridge Central Research Ethics Committee (19/EE/0307), and the Health Research Authority (IRAS268830). Additional approvals were obtained locally as required. The study was registered at clinicaltrials.gov (NCT04673929) as the RECUT study. This manuscript has been prepared with reference to the 'Strengthening the reporting of observational studies in epidemiology' (STROBE) checklist for cohort studies.

Study Design and Setting

A retrospective observational cohort study was undertaken in 16 international tertiary referral units across North America, Europe, and Asia. Centers with a high volume practice and known to use TORS in the management of HNC were invited to participate.

Participants

Eligible patients were aged older than 18 years, with a history of previous HNC treated with (chemo)radiotherapy, who subsequently experienced a residual, recurrent, or new primary HNC that was treated using TORS.

Patients were not eligible if the TORS was performed only for diagnostic purposes or to treat nasopharyngeal or thyroid cancers.

Practices for identifying patients varied by the contributing center, but it was stipulated that consecutive eligible patients must be submitted to limit selection bias. All patients had their TORS performed prior to August 1, 2018, with data submission only accepted after August 1, 2020, to allow an appropriate period for the primary outcome event.

Data Collection

Data were collected by participating sites onto a standardized electronic case report form, created using Excel software (Microsoft Corporation, Redmond, WA, USA). Restricted data fields and data validation were used to improve data completeness and homogeneity. Missing or ambiguous data were queried, and the data point excluded from the relevant analysis if unresolved. Adult Co-Morbidity Evaluation (ACE-27) scores were calculated for comorbidities, and Performance Status Scale for Head & Neck Cancer Patients—Normalcy of Diet (PSS-HN NoD) (14) scores reported swallow function.

Statistical Analysis

The primary outcome was local control (LC) at 2 years. No a priori sample size calculation was performed. Categorical variables were compared using the Fisher exact test and continuous variables using the Wilcoxon test. Time-to-event outcomes (overall survival [OS], disease-free survival [DFS], disease-specific survival, and LC) were estimated using the Kaplan-Meier (KM) method, with subgroups compared using log-rank tests. Endpoints were as follows: death from any cause for OS; diagnosis of residual or recurrent local, regional or distant disease, or death from any cause for DFS; death from residual or recurrent disease for disease-specific survivals; and diagnosis of local residual or recurrent disease for LC. Analyses used the survival and survminer packages in R. A competing events sensitivity analysis was completed for subgroups showing a statistically significant difference in the primary endpoint (LC). Regional recurrence, distant recurrence, and death from any cause were classed as competing events and analyzed with the Gray test using the cmprsk package in R.

Prognostic factors for time-to-event outcomes were assessed using Cox proportional hazards regression analysis. The proportional hazards assumption was assessed using Schoenfeld residuals and visual assessment of the KM curves. Time-

varying coefficients were further assessed using a log(time) interaction, which was adopted if returning a statistically significant, or close to statistically significant, result. The multivariable model was constructed using a backward stepwise elimination process. The initial model was built with variables found to be statistically significant on univariable analysis. At each stage, the least statistically significant variable above the threshold was eliminated until only statistically significant variables remained using a *P* value threshold of less than .05 throughout to denote statistical significance.

Surgical Margin Analysis

Centers were asked for the nearest mucosal and deep surgical resection margins from the main TORS specimen, as recorded on the histopathology report. Positive margins were considered to be equal to 0 mm. For patients who had both mucosal and deep margins reported, the lowest millimeter value was recorded. Where further oncological resection margins were taken, they were orientated and combined with the main specimen resection margin wherever possible. Patient-side biopsies, taken primarily to provide additional information to the multidisciplinary team (MDT) or tumor board that the tumor bed was free from disease (commonly referred to "margins" but not intended as oncological resections), were not considered. Data regarding intraoperative frozen sections were not specifically collected, rather the resultant reports and resection specimens were interpreted according to the methodology above.

Two methods were then used to investigate the optimal cut point of this closest margin, to dichotomize our cohort with the greatest differentiation in LC: maximally selected rank statistics using the full survival data (maxstat package in R) and receiver operator characteristic analysis at 2 years using Youden index (ROCit package in R).

All analyses were performed using RStudio statistical software (RStudio, Boston, MA, USA).

Deviations From the Protocol

The following deviations and clarifications from the published protocol were made: death from any cause was added as an endpoint for DFS, and LC is reported as the primary outcome and to calculate the margin cutoff, in place of disease-free survival. This decision was made prior to any analysis as it was felt it would better reflect the effectiveness of TORS as a treatment for local disease. Confidence intervals (CI) were used in place of prediction intervals for the KM estimates.

Results

Characteristics of the Study Population

Centers and Participants

Data from 306 patients from the 16 participating centers were submitted and reviewed for eligibility. Following strict application of the eligibility criteria, 278 patients were eligible for analysis (median 13 per center; range = 3-49; interquartile range [IQR] = 7.25-23.75). One center maintained reliable records for oropharyngeal cancers only, therefore, only these patients were contributed to ensure data integrity. The following patients were screened out on central eligibility check: no previous head and neck radiotherapy (24 patients); no confirmed malignancy on either pre- or post-TORS histology; (3 patients) and a case of nasopharyngeal cancer (1 patients). The year of the first included patient from each participating center ranged from 2007 to 2017 (median = 2013).

The median age for all patients was 61 (range = 38-93; IQR = 56-69), and 20.1% were female (n = 56 of 279) years. The median follow-up for survivors was 38.5 (range = 0.1-107.5; IQR = 23.5-60.0) months, and for all patients was 28.5 (range = 0.1-107.5; IQR = 13.7-48.7) months.

Clinicopathological characteristics and perisurgical management are shown in Table 1 (and by subgroups in Supplementary Table 1, available online). Histopathological and functional outcomes following TORS, presented for all patients and by subgroups, are shown in Supplementary Table 2 (available online). Supplementary Table 3 (available online) gives details of the previous HNCs for the cohort. The majority had a single previous HNC (86%, n = 240) with 11.5% having had 2 previous cancers (n = 32), and 2.5% having had 3 (n = 7).

Patterns of Disease

The majority of cancers in this cohort were oropharyngeal, representing 93.8% (n = 259 of 276), with tongue base cancers constituting more than half (52.9%, n = 146 of 276) of all patients. Neck disease was identified pre-operatively in 21.5% (n = 58 of 270) of patients, with 60.4% (n = 168 of 278) undergoing some form of neck surgery alongside TORS.

The median time since completion of treatment for the previous HNC was 761.5 days, with 29.3% (n = 79 of 270) of surgeries performed within 1 year and 13.0% (n = 35 of 270) being more than 10 years after initial treatment; 8.5% (n = 23 of 272) were recorded as new primary disease within 5 years of the previous cancer but at a separate site.

Survival Outcomes

Time-to-event analyses are presented for all subjects (Figure 1), by margin status (Figure 2), by human papillomavirus (HPV) status in oropharyngeal disease (Supplementary Figure 1, available online), and by timing of TORS relative to previous HNC (Supplementary Figure 2, available online). For all subjects, the 2-year LC was 69.0% (95% CI = 63.2 to 75.3), and 5-year LC was 62.2% (95% CI = 55.6 to 69.5). Further 2- and 5-year outcomes are summarized in Table 2. Over the study period, there were 83 deaths from disease, 32 deaths from other causes, 82 local recurrences, 24 regional recurrences, and 26 patients with distant metastases.

On log-rank test, there was no statistically significant difference in LC by HPV status in oropharyngeal disease ($P = .43$) or by timing of TORS relative to previous HNC ($P = .51$). However, there was a statistically significant difference in LC by margin status ($P < .001$). Sensitivity analysis corroborated this significance for LC (Cox hazard ratio [HR] = 2.87, 95% CI = 1.66 to 4.96; $P < .001$) and showed no statistically significant difference in competing events (Gray HR = 0.97, 95% CI = 0.57 to 1.66; $P = .90$).

Following TORS, 6.1% of patients had further disease recurrence that was subsequently successfully treated to leave them disease-free (n = 17 of 278): 10 were treated for local disease, 3 for regional metastases, and 4 for distant metastases.

Prognosticators of Time-to-Event Outcomes

Results from univariable analysis are shown in Supplementary Table 4 (available online) and multivariable analysis in Supplementary Table 5 (available online).

The closest surgical resection margin was the only factor to remain statistically significant for all 4 time-to-event scenarios,

Table 1. Details of clinicopathological characteristics, peri-operative management, and nonsurgical oncological therapies, presented for all patients (n = 278)

Characteristics	No. (%)
General	
Age, y[a]	
Data available	278 (100)
Data unknown	0 (0)
31-40	3 (1.1)
41-50	23 (8.3)
51-60	99 (35.6)
61-70	94 (33.8)
71-80	46 (16.5)
81-90	12 (4.3)
91-100	1 (0.4)
Sex	
Data available	278 (100)
Data unknown	0 (0)
Female	56 (20.1)
Male	222 (79.9)
Smoking	
Data available	231 (83.1)
Data unknown	47 (16.9)
Never smoker	61 (26.4)
Ex-smoker	105 (45.5)
Current smoker	65 (28.1)
Alcohol	
Data available	243 (87.4)
Data unknown	35 (12.6)
No alcohol	107 (44)
Light alcohol	87 (35.8)
Heavy alcohol	49 (20.2)
Comorbidities (Adult Co-mobidity Evaluation [ACE-27])	
Data available	220 (79.1)
Data unknown	58 (20.9)
0	76 (34.5)
1	79 (35.9)
2	40 (18.2)
3	25 (11.4)
Previous HNCs[b]	
Number of previous HNC	
Data available	278 (100)
Data unknown	0 (0)
1	239 (86)
2	32 (11.5)
3	7 (2.5)
RT to primary site	
Data available	271 (97.5)
Data unknown	7 (2.5)
Yes	270 (99.6)
No	1 (0.4)
RT to neck	
Data available	249 (89.6)
Data unknown	29 (10.4)
Yes	242 (97.2)
No	7 (2.8)
TORS	
Timing by diagnosis	
Data available	272 (97.8)
Data unknown	6 (2.2)
Residual (<12 mo)	83 (30.5)
Recurrence (12 mo to 5 y)	101 (37.1)
New primary (>5 y)	65 (23.9)
New primary (<5 y, separate site)	23 (8.5)
Timing by time to surgery[a]	
Data available	270 (97.1)
Data unknown	8 (2.9)
0 to 1 y	79 (29.3)
1 to 2 y	53 (19.6)
2 to 3 y	37 (13.7)
3 to 4 y	16 (5.9)
4 to 5 y	16 (5.9)
5 to 6 y	13 (4.8)
6 to 7 y	4 (1.5)
7 to 8 y	7 (2.6)
8 to 9 y	6 (2.2)
9 to 10 y	4 (1.5)
> 10 y	35 (13)
Median, d	761.5
Primary site	
Data available	276 (99.3)
Data unknown	2 (0.7)
Nasopharynx	0 (0)
Tonsil	88 (31.9)
Tongue base	146 (52.9)
Soft palate	11 (4)
Posterior oropharyngeal wall	14 (5.1)
Piriform fossa	7 (2.5)
Post cricoid	1 (0.4)
Posterior hypopharyngeal wall	0 (0)
Supraglottis	9 (3.3)
Glottis	0 (0)
Subglottis	0 (0)
HPV status	
Data available	210 (75.5)
Data unknown	68 (24.5)
Positive	76 (36.2)
Negative	134 (63.8)
Clinical staging	
cT	
Data available	268 (96.4)
Data unknown	10 (3.6)
Tx	0 (0)
T0	0 (0)
Tis	0 (0)
T1	127 (47.4)
T2	120 (44.8)
T3	12 (4.5)
T4	4 (1.5)
T4a	5 (1.9)
T4b	0 (0)
cN	
Data available	270 (97.1)
Data unknown	8 (2.9)
Nx	5 (1.9)
N0	207 (76.7)
N1	31 (11.5)
N2	5 (1.9)
N2a	2 (0.7)
N2b	12 (4.4)
N2c	6 (2.2)
N3	1 (0.4)
N3a	0 (0)
N3b	1 (0.4)

(continued)

Table 1. (continued)

Characteristics	No. (%)
cM	
Data available	267 (96)
Data unknown	11 (4)
Mx	4 (1.5)
M0	261 (97.8)
M1	2 (0.7)
Peri-operative management	
Concurrent neck surgery	
Data available	278 (100)
Data unknown	0 (0)
None	110 (39.6)
ND for access or vessel ligation only	34 (12.2)
Prophylactic ND	82 (29.5)
Therapeutic ND	52 (18.7)
Reconstruction	
Data available	278 (100)
Data unknown	0 (0)
None (secondary intention)	202 (72.7)
Pedicle flap	20 (7.2)
Free flap	56 (20.1)
Tracheostomy	
Data available	277 (99.6)
Data unknown	1 (0.4)
Yes	105 (37.9)
No	172 (62.1)
Gastrostomy	
Data available	278 (100)
Data unknown	0 (0)
Yes	109 (39.2)
No	169 (60.8)
Nonsurgical oncological therapy	
Post-op radiotherapy	
Data available	262 (94.2)
Data unknown	16 (5.8)
None	232 (88.5)
Yes	30 (11.5)
Chemotherapy	
Data available	258 (92.8)
Data unknown	20 (7.2)
None	232 (89.9)
Neoadjuvant	10 (3.9)
Adjuvant	16 (6.2)
Immunotherapy	
Data available	275 (98.9)
Data unknown	3 (1.1)
None	259 (94.2)
Neoadjuvant	7 (2.5)
Adjuvant	9 (3.3)

[a]Compared as continuous data. HNC = head and neck cancer; HPV = human papillomavirus; ND = neck dissection; RT = radiotherapy; TORS = transoral robotic surgery.
[b]See also Supplementary Table 1 (available online).

including LC (HR = 2.87, 95% CI = 1.66 to 4.96; $P < .001$) and OS (HR = 2.51, 95% CI = 1.56 to 4.03; $P < .001$).

Complications

Data on peri-operative complications for TORS were available for 97.8% (n = 272). The post-TORS hemorrhage rate, requiring return to theater, was 8.1% (n = 22 of 272) with a single case of hemorrhage resulting in death. The overall mortality related to the TORS procedures was 1.8% (n = 5 of 272) with the remaining 4 patients dying from chest sepsis (n = 3) and a stroke (n = 1) within 30 days of surgery.

The median time to postoperative hemorrhage was 6 (range = 1-42; IQR = 2-8) days (data available for 19 of 22 bleeds).

Free flap failure was seen in 5.4% (n = 3 of 56), and fistulae were reported in 0.7% (n = 2 of 272). None of these complications were reported in 89.0% (n = 243 of 272) of patients.

Surgical Resection Margin Analysis

Closest surgical resection margin data were available for 194 patients (69.8% of 278 cohort). The closest surgical resection margin was reported as mucosal in 24.7% (n = 48), deep in 49.0% (n = 95), and equal mucosal and deep in 26.3% (n = 51). The positive margin rate was 25.3% (n = 49).

Most margins were reported to whole millimeter values, except 13 patients, which were reported to 1 decimal place (Supplementary Figure 3, available online). The most discriminating cut point for surgical resection margin was found to be no more than 1.0 mm by both methods [maxstat value = 3.919. Area under the curve (AUC) = 0.679, (95% CI = 0.589 to 0.769), sensitivity 69.8% (95% CI = 55.7% to 81.7%), specificity 62.8% (95% CI = 52.2% to 72.5%)]. The 2-year LC around this cut point was 80.9% for more than 1.0 mm and 54.2% for no more than 1.0 mm.

By way of sensitivity analysis, and to explore the implications of selecting different margin cut points, KM analyses were produced for all whole millimeter values from 0 to 5 mm (Supplementary Figures 4-8, available online).

When the closest surgical resection margin was reported as positive (equal to 0 mm), 2-year LC was 48.2% (95% CI = 34.9% to 66.5%) vs 74.6% (95% CI = 67.2% to 82.8%) for all higher values. The greatest separation of 2-year LC was around a cut point of 1.0 mm, with survival of 80.9% (95% CI = 72.8% to 89.8%) more than 1.0 mm and 54.2% (95% CI = 44.1% to 66.1%) no more than 1.0 mm (Figure 2). Increasing the cut point incrementally at millimeter intervals had the effect of reducing the separation of the 2-year LC outcomes. The highest 2-year LC was seen above a cut point of 3 mm, though it should be recognized that the number of patients contributing data at these greater closest surgical resection margin cut points is limited and is reflected in the widening confidence intervals with notable overlaps at these higher cut point values.

Functional Outcomes

Peri-Operative

Peri-operative tracheostomy and gastrostomy rates are shown in Supplementary Table 2 (available online). Tracheostomies were used at the time of TORS in 37.9% (n = 105 of 277) of patients and gastrostomies in 39.2% (n = 109 of 278). Overall rates at 1 year for all subjects were 10.8% (n = 21 of 195) for tracheostomy usage and 33.8% (n = 66 of 195) for gastrostomy usage.

At the time of last follow-up, 74.7% were tolerating soft chewable foods or better (PSS-HN NoD score ≥ 50, n = 68 of 91), and 4.4% were taking no oral diet (PSS-HN NoD score = 0, n = 4 of 91) (median follow-up 43.0 months; range = 0.1-107.5; IQR = 26.5 to 62.3).

Outcomes in Patients Disease-Free at 1 Year

There were 188 patients with no evidence of local recurrence who were followed up for more than 1 year. For these patients,

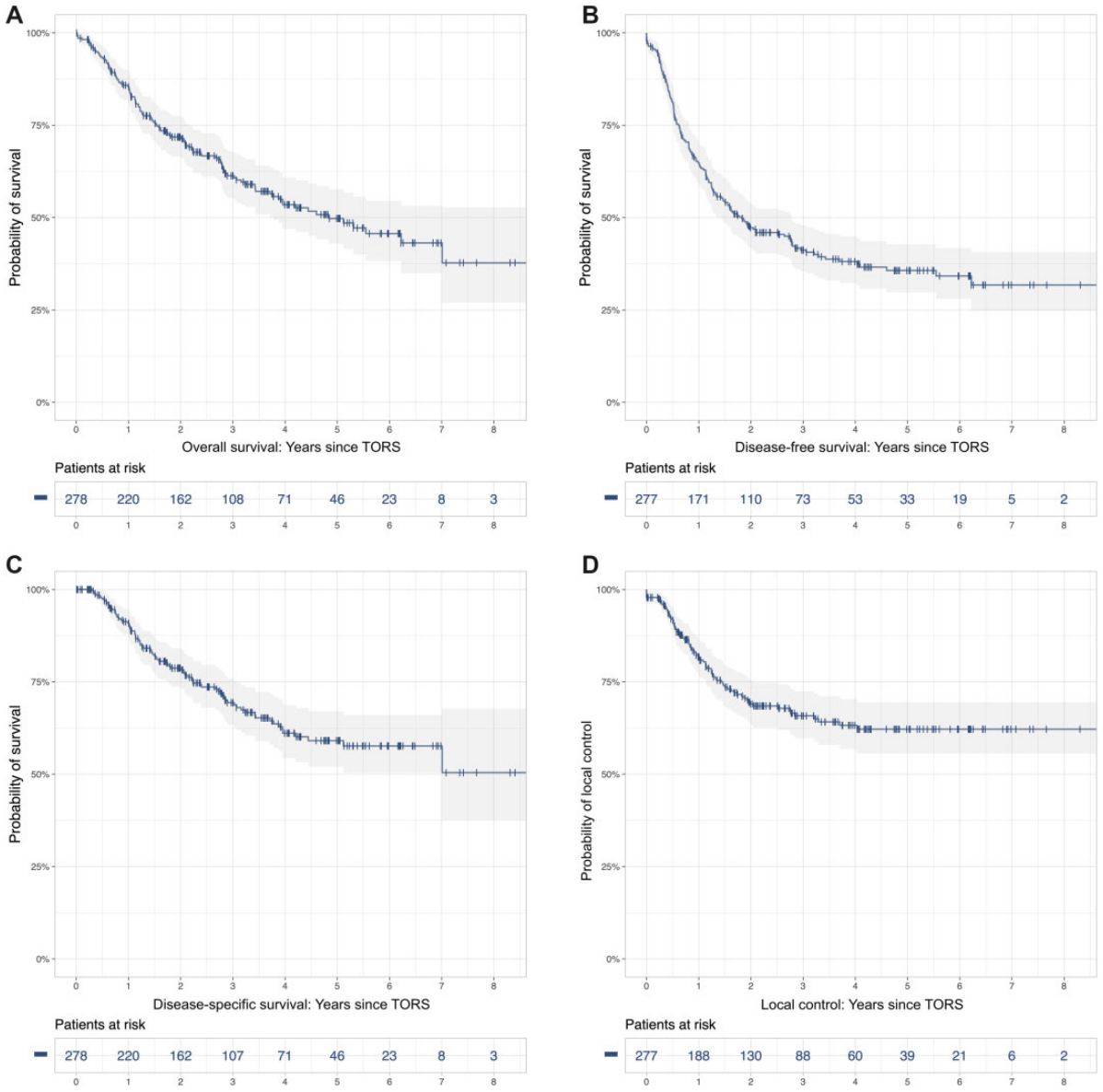

Figure 1. Kaplan-Meier survival estimates for all subjects. A) overall survival; (B) disease-free survival; (C) is disease-specific survival; (D) local control. TORS = transoral robotic surgery.

the change in tracheostomy rates, gastrostomy rates, and PSS-HN NoD scores at baseline and at 1 year were available for 90.4% (n = 170 of 188) and 42.6% (n = 80 of 188), respectively. The changes in status for these variables are visualized in Sankey plots in Figure 3. The majority (92.9%) of patients were tracheostomy free at 1 year, 67.6% were gastrostomy free, and 73.8% were tolerating a soft diet or better on PSS-HN NoD score following TORS (score ≥50).

Discussion

This study provides evidence, from individual patient data contributed by multiple international tertiary referral centers, that supports the use of TORS to treat HNCs in previously irradiated fields. The survival and functional outcome data presented corroborate the findings of previous smaller studies and a previous meta-analysis on the topic (15-17). OS in this cohort was 71.8% at 2 years and 49.8% at 5 years, which compares favorably to alternative treatments that may be considered for these patients including re-irradiation and open surgery. It is accepted that direct comparisons between studies and treatment modalities are difficult in the absence of randomized studies and that, generally, patients undergoing surgery are more likely to have smaller volume, lower-stage disease, with a performance status, which may tolerate the physiological strains of a general anesthetic (18).

Various studies reporting re-irradiation with intensity-modulated radiotherapy (IMRT) record 2-year OS around 40% to 50%, albeit at the expense of severe acute toxicity in around a quarter of patients (5,19,20), though the majority of these patients may have been considered unsuitable for attempted surgery with curative intent. Ward et al. (6) considered patients undergoing salvage surgery in addition to re-irradiation with intensity-

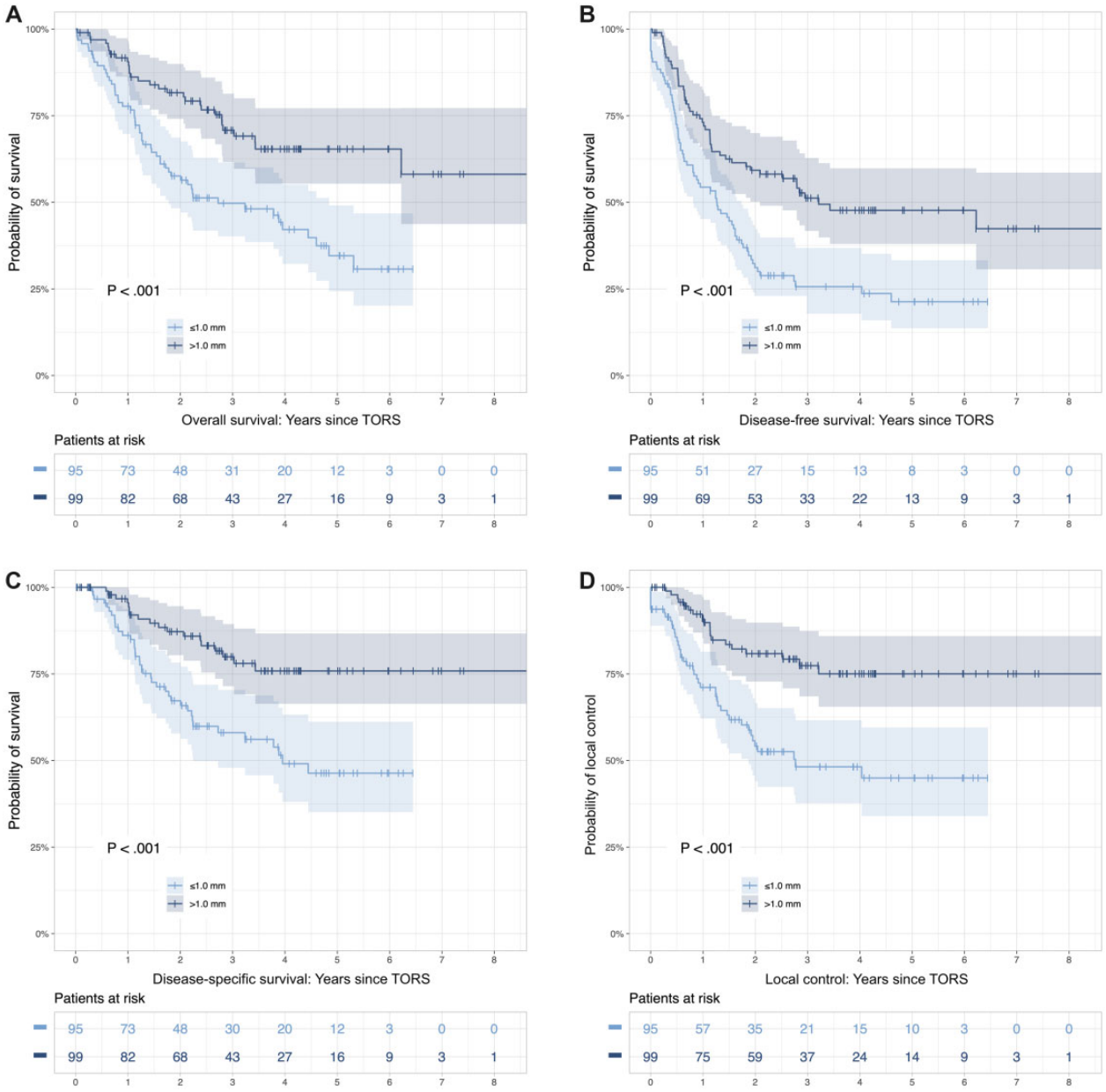

Figure 2. Kaplan-Meier survival estimates by margin status around a >1.0 mm cut point (*P* value given for log-rank test). A) overall survival; (B) is disease-free survival; (C) disease-specific survival; (D) local control. TORS = transoral robotic surgery.

modulated radiotherapy and reported 2-year OS of 61.9%, although this cohort would have included patients undergoing open procedures too based on the tumor subsites presented.

Comparisons with open salvage surgery alone are also favorable. For example, Patel et al. (3) reported 5-year DFS of only 19% compared with 35.7% in the present series. Additionally, Hamoir et al. (4) reported markedly lower OS for their oropharyngeal patients treated with salvage surgery, with a 2-year rate of 51.9% (95% CI = 38.1 to 70.7) compared with 71.8% (95% CI = 66.5 to 77.5) in this series and a 5-year rate of 29.3% (95% CI = 17.1 to 50.1) compared with 49.8% (95% CI = 43.0 to 57.7) presented here. Again, it is important to recognize that these open surgery patients may have had more advanced disease, in different head and neck subsites, than those undergoing transoral surgery.

The functional outcomes presented here compare favorably to open surgery alternatives, with only 37.9% and 39.2% perisurgical tracheostomy and gastrostomy rates, respectively, compared with 79% and 75% reported previously by White et al. (15). Further comparisons between studies are challenging because of the lack of consistent reporting of standardized measures of swallowing. However, even in isolation, the high rate (73.8%) of disease-free patients tolerating a soft diet or better on PSS-HN NoD score at 1 year postsurgery, is in support of TORS in this population.

HPV status, largely based on immunohistochemistry for p16 as a surrogate, was available for 75.5% of eligible squamous cell carcinomas (SCCs), with 62.3% of oropharyngeal SCCs being reported as HPV negative (n = 124 of 199). There was no statistically significant distinction between the survival curves by HPV status for any of the 4 time-to-event analyses presented herein (Supplementary Figure 1, available online). In the primary setting, HPV status has a statistically significant impact on OS,

Table 2. Oncological outcomes following TORS, presented for all subjects and by subgroups[a]

Oncological status	All patients, % (95% CI)	OPSCC HPV positive, % (95% CI)	OPSCC HPV -negative, % (95% CI)	Closest margin ≤1.0 mm, % (95% CI)	Closest margin >1.0 mm, % (95% CI)	<1 year from previous cancer to TORS, % (95% CI)	≥1 year from previous cancer to TORS, % (95% CI)
At 2 y							
OS	71.8 (66.5 to 77.5)	75.2 (65.6 to 86.2)	72.2 (64.5 to 80.9)	57.6 (48.3 to 68.7)	81.6 (74.1 to 89.9)	60.4 (50.1 to 72.8)	75.8 (69.7 to 82.4)
DFS	47.2 (41.6 to 53.7)	45.9 (35.6 to 59.1)	47.1 (38.9 to 57.1)	31.2 (23.0 to 42.3)	59.3 (50.2 to 70.0)	39.6 (30.0 to 52.3)	50.6 (43.8 to 58.6)
DSS	78.7 (73.7 to 84.1)	81.3 (72.3 to 91.5)	77.8 (70.3 to 86.1)	67.3 (57.8 to 78.3)	87.2 (80.4 to 94.6)	67.0 (56.6 to 79.4)	83.0 (77.4 to 88.9)
LC	69.0 (63.2 to 75.3)	68.5 (57.8 to 81.2)	69.4 (61.0 to 79.0)	54.2 (44.1 to 66.6)	80.9 (72.8 to 89.8)	66.7 (56.1 to 79.4)	70.1 (63.3 to 77.5)
At 5 y							
OS	49.8 (43.0 to 57.7)	58.8 (46.7 to 74.1)	50.6 (40.8 to 62.8)	34.6 (24.3 to 49.1)	65.4 (55.4 to 77.2)	42.3 (31.1 to 57.4)	51.2 (42.9 to 61.1)
DFS	35.7 (29.8 to 42.8)	34.4 (24.4 to 48.4)	38.8 (30.4 to 49.5)	21.3 (13.6 to 33.3)	47.7 (38.0 to 59.8)	33.4 (24.2 to 46.2)	35.3 (27.8 to 44.8)
DSS	59.1 (52.1 to 67.0)	71.3 (59.8 to 85.0)	56.3 (45.9 to 69.1)	46.4 (35.1 to 61.2)	75.9 (66.4 to 86.7)	48.3 (36.1 to 64.6)	62.5 (54.3 to 72.0)
LC	62.2 (55.6 to 69.5)	58.5 (46.4 to 73.7)	64.9 (55.8 to 75.4)	45.0 (34.0 to 59.5)	75.0 (65.5 to 85.9)	64.2 (53.2 to 77.6)	60.9 (52.7 to 70.2)

[a]CI = confidence interval; DFS = disease-free survival; DSS = disease-specific survival; HPV = human papillomavirus; LC = local control; OS = overall survival; OPSCC = oropharyngeal squamous cell carcinoma; TORS = transoral robotic surgery.

with HPV-negative oropharyngeal SCCs faring worse overall (21). In residual and recurrent cases, the influence of HPV status is less clear (22). Fakhry et al. (23) presents a comparison of outcomes in patients who have experienced disease progression in oropharyngeal squamous cell carcinoma initially treated under RTOG 0129 and 0522. Outcomes in their analyses were better for their HPV-positive cases, though overall, their cohort had higher incidence of both residual disease and regional or distant metastases, limiting comparability. The lack of differentiation in survival based on HPV status in the present study may be explained by a change in the biological behaviors of these cancers having been subjected to radiation (24,25).

Details of surgical resection margins were available for 69.8% of our cohort. Using a data-driven approach, it was shown by 2 methods that the most discriminating cut point for the closest surgical resection margin (with local disease control as the outcome) was achieved with groups of no more than 1.0 mm and more than 1.0 mm. Dichotomizing the cohort around this cut point moved the combined cohort's 2-year LC from 69.0% (95% CI = 63.2 to 75.3) to 54.2% (95% CI = 44.1 to 66.6) for those with no more than 1.0 mm and 80.9% (95% CI = 72.8 to 89.8) for those more than 1.0 mm. The margin status around this cut point was the only factor to remain statistically significant on multivariable analysis for all 4 time-to-event scenarios investigated (Supplementary Table 5, available online). Understandably, it may be asked whether a greater margin would improve outcomes further, and this is explored in the Supplementary Figures (available online). It is noted that minimum resection margins at millimeter values of more than 1.0 mm do appear to yield additional protection from local recurrence. However, the impact is incremental, and these estimates should be interpreted with caution as the data around these cut points become more scarce and statistical confidence reduces as the millimeter increases.

It is important to stress that the authors are not recommending that surgeons should aim for more than 1.0 mm minimum resection margins as routine practice for recurrent cancer TORS; surgeons should continue to strive for higher minimum margins where safely feasible and appropriate. However, the results presented here indicate that favorable outcomes can be achieved even when minimum margins are reported as being more than 1.0 mm. With a paucity of effective, alternative, curative-intent treatments for these patients, the prospect of a narrow resection margin at TORS, where otherwise complete resection is felt feasible, should not deter clinical teams from offering such an intervention to this patient group.

The authors acknowledge limitations to the methodology and findings of this study. First, this is an observational study without random assignment of subjects. As such, there will inevitably be an inherent selection bias in the participants included. However, the comprehensive reporting of clinicopathological characteristics from this multicenter consecutive cohort should allow the meaningful translation of outcomes to similar patients across multiple settings. Second, there was no centralized pathological review for the included cases with the local assessment instead being relied on to determine histopathological classification and margin status. Third, margin status was not available for all patients (69.8%).

To conclude, analysis of individual patient data, from multiple international institutions, has shown favorable survival and functional outcomes from TORS used for the management of residual, recurrent, and new primary HNC in previously irradiated fields. In these selected patients, who predominantly have early stage recurrent oropharyngeal SCCs, serious complications from TORS were not common, and functional results were appreciable but acceptable. The required surgical resection margin in these patients may be narrower than previously thought, and concerns about potential narrow margins should not, in themselves, be a contraindication to consideration for TORS.

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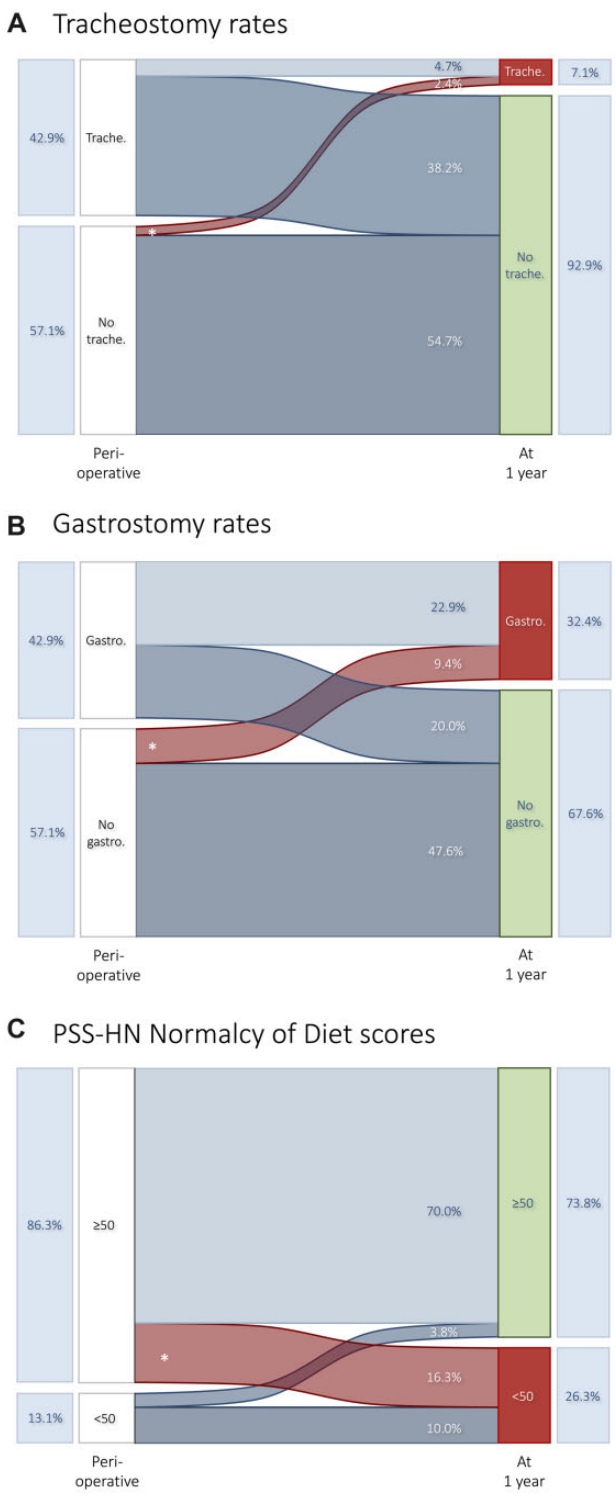

Figure 3. Sankey plots showing functional outcomes for patients free from local disease recurrence at baseline and at 1-year follow-up. A) tracheostomy rates, (B) gastrostomy rates, and (C) PSS-HN normalcy of diet scores. The tranche marked with an * indicates patients who had tracheostomies or gastrostomies placed at a time following the TORS procedure or who had worsening of PSS-HN normalcy of diet scores. Gastro = gastrostomy; PSS-HN = Performance Status Scale for Head and Neck Cancer Patients; TORS = transoral robotic surgery; Trache = tracheostomy.

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Author contributions (CRediT): JH: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, validation, visualization, writing—original draft, and writing—review and editing. EG and LP: methodology, formal analysis, writing—review and editing. KH and CH: conceptualization, formal analysis, supervision, validation, visualization, writing—review and editing. VP: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, and writing—review and editing. GB, ABe, ABo, GD, SB, JDA, UD, PF, TG, PG, NG, DH, CK, MHHL, DL, JSM, JM, BM, EM, GP, SR, NR, CS, AS, MT, KVA, VVP, EW, AB, HS, SS, JR: data curation, investigation, validation, writing—review & editing.

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Data Availability

The data underlying this article cannot be shared publicly due to a combination of restrictions relating to local data sharing laws and the specific data sharing agreements that were put in place to allow this cohort to be compiled. The data will be shared following reasonable request to the corresponding author, who will raise the request with the project management

team for permission to make the data available, which will take place in a secure environment in compliance with our existing legal constraints.

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