Primary transoral robotic surgery +/- adjuvant therapy for oropharyngeal squamous cell carcinoma—A large observational single-centre series from the United Kingdom

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Abstract

Objectives: To analyse the oncological outcomes following primary Transoral Robotic Surgery (TORS) for oropharyngeal squamous cell carcinoma (OPSCC).

Design: Observational case series.

Setting: Tertiary centre; first TORS practice to commence in the UK.

Participants: All consecutive patients undergoing primary TORS with curative intent, with or without adjuvant treatment.

Main outcome measures: Descriptive analysis of patient and tumour pathology variables. Survival outcomes: Overall, Disease-Specific, Progression-Free and Locoregional control.

Results: The cohort comprised of 120 patients undergoing TORS with minimum 12-month follow-up data and the following characteristics: mean age 58 years, 91 males (76%), 78 tonsil (65%) and 34 base of tongue primaries (28%), 89% HPV-related OPSCC. The surgical pathology revealed 14 (12%) with positive margins, 19 (16%) had close margins <2mm and 31% with extranodal extension. The treatment was as follows: 39 (33%) treated with TORS alone, 50 (42%) received adjuvant radiotherapy and 31 (26%) received adjuvant radiotherapy with chemotherapy. There were 15 recurrences. Estimated survival for all patients at 3 years (95% CI): overall 85% (78-92), disease-specific 90% (85-96), progression-free 86% (79-92) and locoregional control 90% (84-96). The equivalent survival figures for the HPV-related cases alone were as follows: overall 88% (82-94), disease-specific 93% (87-98), progression-free 88% (81-95) and locoregional control 92% (87-98).

Conclusions: Whilst TORS has become a common practice in the management of OPSCC in the UK, these are the first reported oncological outcomes. For selected patients, TORS with or without adjuvant therapy is an appropriate treatment modality.
1 | INTRODUCTION

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) doubled in the United Kingdom (UK) between 2002 and 2011 and appeared to rise equally for both Human Papilloma Virus (HPV)-related tumours and HPV negative tumours.\(^1\) Approximately half of OPSCC is HPV-related in the UK.\(^1\) Non-surgical management using radiotherapy, with concurrent chemotherapy where indicated, was the primary treatment modality for the majority of patients (56%) in 2014.\(^2\) During the evolution of TORS for OPSCC, reports suggested equivalent oncological outcomes when TORS was compared with modern radiation techniques, through case series comparisons.\(^3\) This team’s philosophy at Newcastle-upon-Tyne Hospitals (NuTH) has focussed on minimising functional impairment whilst maintaining oncological effectiveness. TORS, and previously transoral laser microsurgery (TLM), has formed the basis for this philosophy for selected patients. Lateralised, small volume, resectable OPSCC tumours, with no or ipsilateral nodal disease, have been offered primary surgical management. The potential staging benefits of contralateral neck dissections within this treatment philosophy and the swallowing outcomes following primary TORS and TLM have been published previously.\(^4\)\(^-\)\(^8\) However, the recently published ORATOR trial—a phase II randomised trial of primary TORS versus radiotherapy ± chemotherapy for OPSCC with 1 y swallowing outcomes as the primary outcome—showed superior swallowing outcomes in the non-surgical group.\(^9\) Whilst the superior swallowing outcome was below the defined threshold equating to a clinically meaningful difference, the results from this sole randomised clinical trial in the field of OPSCC primary management require TORS practitioners to assess their outcomes in detail. This study aimed to analyse the oncological outcomes following primary TORS for OPSCC. NuTH set up the first TORS programme in the UK. This analysis will offer the first UK reported TORS outcomes for OPSCC.

2 | METHODS

2.1 | Patients

The transoral robotic surgical practice commenced in March 2013 at the Freeman Hospital, Newcastle-upon-Tyne. To date, 229 TORS procedures have been performed, for a variety of upper aerodigestive pathology. Strict inclusion and exclusion criteria were used for this analysis of outcomes. All patients were managed through the multidisciplinary clinic.

Inclusion criteria: Consecutive cases of squamous cell carcinoma of the oropharynx (OPSCC), where TORS was the primary definitive treatment modality, with a minimum of 12-month follow-up. Patients who underwent diagnostic TORS tongue base mucosectomy (TBM) were only included if it permitted adjuvant dose radiotherapy (as opposed to radical dose radiotherapy to the oropharynx as primary treatment) or avoided base of tongue irradiation (if the TBM specimen showed no cancer, along with negative tonsillectomy, or a very small primary tumour where clearance was achieved with the TBM—both situations in conjunction with neck dissection(s)).

Exclusion criteria: Non-OPSCC. Recurrent or second primary OPSCC. TORS employed for diagnosis (eg TBM without neck dissection), with radical dose radiotherapy ± chemotherapy as the primary modality.

2.2 | TORS

Surgical resection of the primary tumour was performed using the da Vinci surgical robot (Intuitive Surgical Inc) following previously published descriptions.\(^10\)\(^-\)\(^12\) A standard lateral oropharyngectomy was performed for primary tonsil, lateral oropharyngeal wall tumours and for the remaining tonsil bed following diagnostic tonsillectomy. A standard tongue base hemiglossectomy was performed for all known base of tongue tumours. Bilateral tonsillectomy and base of tongue mucosectomy were performed as part of the diagnostic workup for an unknown primary tumour. All specimens were meticulously orientated for pathological examination.\(^13\) All patients underwent either ipsilateral or bilateral selective neck dissection—the clinical rationale for bilateral neck dissection in lateralised OPSCC in this unit has been described.\(^4\) Primary tumour specimens were assessed for p16 immunohistochemistry followed by high-risk HPV in situ hybridisation, as per current guidelines.\(^14\)\(^,\)\(^15\)

2.3 | Adjuvant oncological treatment

The gross tumour volume (GTV) covered the TORS tumour bed. An additional 10 mm defined the clinical target volume (CTV), to include
the primary site and involved neck node levels. The CTV was edited for air cavities and anatomical barriers such as bone. A further, standard fixed margin of 5 mm for 3D conformal radiotherapy (3D RT) or 3 mm for intensity-modulated radiotherapy (IMRT) was added to define the planning target volume (PTV). The radiotherapy dose was 60-65 Gy in 30 fractions over 6 wk. In patients with resection margins ≥2 mm and no extranodal extension (ENE), 60 Gy radiotherapy was given. In patients where resection margins were close or positive, 63-65 Gy radiotherapy was given. In cases with pN0, no adjuvant radiotherapy was given to the neck. The indications for the addition of concomitant chemotherapy were either positive surgical margins or the presence of ENE. The chemotherapy regimen consisted of cisplatin 40 mg per metre squared (with a capped dose of maximum 70 mg) on a weekly basis for 6 wk. The approach to T0 patients, following base of tongue mucosectomy evolved very early through the study period reaching a consensus to avoid primary site irradiation.

### 2.4 | Outcome measures

The demographic outcomes collected were as follows: age at date of surgery, sex, smoking status—current, non-smoker or ex-smoker (defined as stopping within 2 y). The pathological outcomes collected were as follows: margin status, lymphovascular invasion (LVI), perineural invasion (PNI), ENE and HPV status. Stage was recorded according to both UICC TNM 7 and TNM 8 systems. To assess margin status, the closest margin was recorded irrespective of whether this was at a mucosal margin or deep margin. Where separate, labelled and oriented margins were resected, these were combined with the main tumour specimen margins. The margins were grouped as 0 = involved / tumour at margin, 0.1mm - 0.9mm, 1.0 - 1.9mm, 2.0 - 4.9mm, 5mm or greater, or “clear TORS resection” (ie a diagnostic tonsillectomy, a diagnostic biopsy of a small base of tongue lesion or a base of tongue mucosectomy with a tumour detected, followed by a planned definitive TORS resection—lateral oropharyngectomy or base of tongue hemiglossectomy—which was subsequently free of residual carcinoma following pathological analysis).

### 2.5 | Statistical analysis

Descriptive statistics were used to display the patients' demographics and tumour pathology. The distribution of margin status for the different tumour subsites was analysed with the Chi-squared test. The survival outcomes of interest were defined as overall survival (OS), disease-specific survival (DSS), progression-free survival (PFS) and locoregional control (LRC). Estimated 2-year and 3-year survival data were calculated from Kaplan-Meier survival tables with plots used for graphical representation. The 95% confidence intervals for survival were calculated as mean ± 1.96 x standard error. The log rank test was used to assess the association of co-variates to survival within the Kaplan-Meier analysis. The association of co-variates to survival outcomes was explored with univariate and subsequent multivariable Cox regression.

### 3 | RESULTS

The analysis included data for 120 consecutive patients meeting the eligibility criteria treated between March 2013 and May 2019. Nineteen patients who underwent diagnostic TBM went on to receive definitive non-surgical therapy and were excluded from the analysis. These patients were not included in the 120. Seven patients with a negative TBM were included (pT0). None of these patients received irradiation to the base of tongue: two were treated with surgery alone, three received neck irradiation and two received neck irradiation with chemotherapy for ENE. The data set was complete other than missing data for the smoking status of one patient, who died of other causes. The mean follow-up to the last appointment or death was 33.3 mo (SD 19.0). Median follow-up was 33.0 mo (range 12 to 85, interquartile range 17 to 49). Three patients required a return to theatre to manage major postoperative haemorrhage. No tracheostomies were performed in any of the 120 patients. The patient demographics, pathological staging and pathological characteristics are shown in Table 1. The UICC TNMB pathological staging for the HPV-related cases is shown in Table 2. The pathological margin categories are presented in Table 3. There was no statistically significant difference in margin categories between lateral oropharynx and base of tongue tumour resections (χ² P =.10).

No adjuvant therapy was given to 39 patients (33%), 50 (42%) received radiotherapy and 31 (26%) were treated with radiotherapy and chemotherapy. Of the 39 patients, three patients declined adjuvant therapy after discussions. Two patients were unfit to receive any adjuvant therapy.

Fifteen patients developed a recurrence following treatment: four local, five regional, one local and regional, and five patients developed distant metastases. One patient developed a second primary tumour. At the census date, 99 patients (82.5%) were alive with no evidence of disease, one was alive with disease, 11 (9.2%) died of disease and 9 (7.5%) died of other causes. There were three deaths in the treatment period which were as follows: one patient died in the postoperative period as a result of gallstone-induced pancreatitis and multi-organ failure: one patient, aged 79, died of respiratory failure 5 wk postoperatively: one patient developed heart failure during adjuvant radiotherapy. The estimated 3-year survival data are presented in Table 4. The details for individual patients with recurrent disease are presented in Table 5. The Kaplan-Meier survival analysis and log rank tests demonstrated that when all 120 patients were grouped according to TNM 7, the survival outcomes were not statistically different according to overall stage: OS, log rank P =.88, DSS P =.92, PFS P =.65, LRC P =.39. HPV status was associated with OS—log rank test P <.001, DSS P =.008, PFS P =.044 and LRC P =.05.
When assessing the HPV-related cases alone (n = 107), all patients had either stage I or II disease according to TNM 8. Kaplan-Meier survival plots (Figure 1) and log rank testing demonstrated that OS and DSS differed between stage I and II, log rank $P = .029$ and $P = .04$, respectively, but PFS and LRC did not: $P = .2$ and $P = .43$. Patients in stage II had superior LRC than stage I, as all 3 recurrences in the stage II group were distant metastases.

On univariate Cox regression analysis, risk factors for locoregional or distant recurrence in all patients were smoking status ($P = .02$), perineural invasion ($P = .03$) and a trend for HPV negative tumours to recur ($P = .056$). However, no patient or tumour factors were risk factors for recurrence on a multivariable Cox regression analysis including the above factors. For the HPV-related cases, only smoking status was a risk factor for any type of recurrence ($P = .042$). TNM stage I or II was not a risk factor for locoregional or distant recurrence when combined together.

4 | DISCUSSION

These are the first oncological outcomes following primary TORS for OPSCC reported in the UK. The survival outcomes would appear consistent with similar large transoral surgical cohorts. The most pertinent data to compare our oncological outcomes with is that of de Almeida et al., who performed similar analyses on 410 patients undergoing TORS across several international centres. Whilst the data came from all patients undergoing TORS, 89% had OPSCC. The inclusion criteria for the present analysis were strict, and most patients who underwent diagnostic TORS were excluded because they received radical doses of radiotherapy. The 3-year disease-specific survival rates from the multicentre analyses were 92.5% (95%CI, 87.8%-95.5%). Our equivalent figure was 90% (85-96), and 93% for the HPV-related group. We noted no

### TABLE 1  Demographic details and pathology data for all patients (n = 120)

| Age       | Mean | Range |
|-----------|------|-------|
| Sex       | Male (%) | 91 males (76%) | Female (%) | 29 females (24%) |
| Tumour site | Lateral Oropharyngeal Wall | 78 (65%) | Base of Tongue | 34 (28%) | Unknown Primary | 7 (6%) | Posterior Pharyngeal Wall | 1 (1%) |
| pT category (TNM 7 and 8) | T0 | 7 (6%) | T1 | 53 (44%) | T2 | 58 (48%) | T3 | 2 (2%) |
| pN category (TNM 7) | N0 | 22 (18%) | N1 | 23 (19%) | N2a | 23 (19%) | N2b | 37 (31%) | N2c | 6 (6%) | N3 | 9 (7.5%) |
| pStage (TNM 7) | I | 8 (6.7%) | II | 15 (12.5%) | III | 20 (16.7%) | IVA | 77 (64.2%) |
| Smoking status | Non-smoker | 92 (77%) | Current smoker | 24 (19%) | Ex-smoker | 4 (3%) |
| HPV status | Positive | 107 (89%) | Negative | 13 (11%) |
| LVI | No | 73 (61%) | Yes | 47 (39%) |
| PNI | No | 108 (90%) | Yes | 12 (10%) |
| ENE | No | 83 (69%) | Yes | 37 (31%) |

### TABLE 2  Pathological stage for HPV-related cases according to TNM 8 (n = 107)

| Tumour Site | Lateral Oropharyngeal Wall | 69 (65%) | Base of Tongue | 33 (31%) | Unknown Primary | 5 (5%) |
| pT category | T0 | 5 (5%) | T1 | 50 (47%) | T2 | 50 (47%) | T3 | 2 (2%) |
| pN category | N0 | 17 (16%) | N1 | 81 (76%) | N2 | 9 (8%) |
| pStage | I | 98 (92%) | II | 9 (8%) |

### TABLE 3  Margin Data

| Length of Margin | Number of patients | % |
|------------------|--------------------|---|
| 0                | 14                 | 11.7 |
| 0.1 - 0.9mm      | 5                  | 4.2 |
| 1.0 - 1.9mm      | 14                 | 11.7 |
| 2.0 - 4.9mm      | 50                 | 41.7 |
| 5.0mm or greater | 10                 | 8.3 |
| Clear TORS resection | 27                | 22.5 |
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**TABLE 4** Estimated 3-year oncological outcomes for all patients (n = 120) and HPV-related cases only (n = 107)

| Outcome                              | Estimated 3-year % (95% CIs) for all patients | Estimated 3-year % (95% CIs) for HPV related cases |
|--------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Overall Survival                     | 85 (78-92)                                   | 88 (82-94)                                   |
| Disease-Specific Survival            | 90 (85-96)                                   | 93 (87-98)                                   |
| Progression-Free Survival            | 86 (79-92)                                   | 88 (81-95)                                   |
| Locoregional Control                 | 90 (84-96)                                   | 92 (87-98)                                   |

**TABLE 5** Details for patients with recurrent disease

| Age | Tumour stage | HPV status | Closest TORS margin (mm) | Adj (C)RT | Recurrence detail | Treatment | Disease Status |
|-----|--------------|------------|--------------------------|-----------|-------------------|-----------|----------------|
| 55  | T1N1         | Pos        | 2 – CiS at margin        | No        | Small persistent BoT disease after 3 mo | RT        | Alive and free of disease |
| 63  | T2N1         | Pos        | 0                        | Patient declined | Local lateral OP recurrence on surveillance CT at 20 mo | RT        | Alive and free of disease |
| 60  | T2N0         | Pos        | 2                        | Declined | Local recurrence at 24 mo | Open surgery and CRT | Alive and free of disease |
| 64  | T2N2b        | Pos        | 0                        | Medically unfit to receive RT | Local and regional recurrence at 13 mo | RT (palliation) | Died of disease at 15 mo |
| 58  | T1N1         | Pos        | 4.5                      | Declined | Retropalatine node on surveillance scan at 11 mo | RT        | Alive and free of disease |
| 46  | T2N1         | Neg        | 4                        | No        | Retropalatine node after 13 mo | RT        | Died of disease at 17 mo |
| 59  | T2N0         | Pos        | 5                        | No        | Aggressive regional recurrence after 6 mo, then cerebral metastases. | RT        | Died of disease at 11 mo |
| 65  | T2N2c        | Pos        | 0                        | Yes       | Regional recurrence at 5 mo | Palliation | Died of disease at 18 mo |
| 57  | T0N3         | Pos        | N/A                      | Yes       | Distant metastases at 19 mo | Palliation | Died of disease at 20 mo |
| 58  | T2N2b        | Pos        | 4                        | Yes       | Vertebral metastases at 6 mo | Palliative RT | Died of distant metastases at 16 mo |
| 61  | T1N2b        | Pos        | 6                        | Yes       | Lung metastases at 13 mo, Brain metastases at 28 mo | Stereotatic radiotherapy to lung | Alive with disease |
| 73  | T1N0         | Pos        | 2                        | No        | Distant hepatic and bone metastases at 4 mo | Chemotherapy (palliation) | Died of disease at 5 mo |
| 39  | T1N2c        | Neg        | 0                        | Yes       | Local recurrence in hypopharynx after 18 mo | Pharyngolaryngectomy | Died of disease at 22 mo |
| 54  | T0N3         | Neg        | N/A                      | Yes       | Regional and distant metastases at 4 mo | Palliation | Died of disease at 6 mo |
| 44  | T2N2c        | Neg        | 0.2                      | Yes       | Lung metastases at 17 mo | Monitored with delayed chemotherapy and RT | Died of disease at 46 mo |

Abbreviation: Pos = HPV positive, Neg = HPV negative, N/A = not applicable (no primary tumour located), CiS = carcinoma-in-situ, RT = radiotherapy

disease-related recurrence or deaths after 24 mo post-TORS. A recently published cohort of 264 patients with OPSCC undergoing transoral laser microsurgery in Liverpool, the UK, had a lower proportion of HPV-related cases (66%) than the present cohort (89%). The 5-year DSS for the HPV group was 93% and 86% for all patients. (This reference will need adding at the review of proof stage if accepted for publication—the manuscript has recently been accepted by the European Journal of Surgical Oncology—personal communication at present) The results from the Eastern Cooperative Oncology Group (ECOG) trial 3311 have been published in a conference abstract format. This trial assessed oncological outcomes for patients with HPV-related OPSCC (measured by p16 immunohistochemistry), with intermediate risk factor patients randomised into de-intensified (group B) and standard
The definitions regarding adequate TORS margins are not clear. de Almeida et al quote a 9.9% involved margin rate in their USA multicentre analysis.18 Our involved margins were 11.7%, but a further 4.2% had between 0.1 and 1.0mm margins. Whilst the margin rate <1mm is greater than we would hope, this is a reflection of a pragmatic approach taken by our multidisciplinary team. In the presence of nodal disease with ENE and involved margins, further TORS to achieve clear margins would be inappropriate as it would not alter the recommendation to offer chemoradiotherapy in the adjuvant setting.

The ORATOR trial’s results cast some doubt on our treatment philosophy to offer TORS to this patient population,9 with the ultimate aim to reduce treatment-related functional impairment. Questions have been raised as to how closely the ORATOR TORS group represented normal practice.20 Certainly, using tracheostomies to reduce bleeding risks following TORS could impair swallowing function. The primary outcome MD Anderson Dysphagia

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**FIGURE 1** Kaplan-Meier Survival Plots according to p Stage—TNM 8 for the HPV-related cases (n = 107)
Inventory (MDADI) scores at 12 mo were 80.1 in the TORS group and 86.9 in the radiotherapy group. We have previously published MDADI scores at 12 mo for transoral surgery (both TORS and TLM) followed by radiotherapy alone—82.3, and followed by radiotherapy with chemotherapy—75.4.8 Our results would be in keeping with the ORATOR findings. The standout result from ORATOR is the radiotherapy group’s MDADI score. We have noted such high scores only from reports of induction chemotherapy and radiotherapy trials.21

The present analysis offers further evidence that TORS and adjuvant therapy are oncologically sound. The ECOG 3311 trial has shown that reducing the dose of adjuvant radiotherapy for intermediate risk HPV OPSCC is safe. The PATHOS trial will offer further evidence on that group of patients and will also address the role of chemotherapy in addition to radiotherapy for the high risk group (involved/ close margins and ENE).22 In the near future, the role of TORS in the management of OPSCC will be defined more clearly.

4.1 | Strengths and weakness

The present analysis on consecutively treated patients was based on a near complete data set, with only one missing data item. Tight inclusion criteria were devised prior to data analysis. The results therefore reflect accurate oncological outcomes for this very select group of patients undergoing primary TORS for OPSCC.

The ability to draw conclusions on the underlying patient and tumour variables and their effect on disease recurrence is very limited. A low number of events (recurrence or death) preclude multivariable survival analysis. The univariate Cox regression showed current smokers and patients with perineural invasion were at greater risk of recurrence, with HPV status suggested as a risk factor—although this was a significant factor on log rank testing. Both smoking and HPV status are well-recognised risk factors for survival outcomes following OPSCC treatment.23 Perineural invasion could be a potential risk factor to explore further on a greater sample size.

5 | CONCLUSIONS

This is the largest single-centre analysis to report on oncological outcomes following primary TORS in the UK. The oncological survival and locoregional control outcomes appear to compare well with other large published series for TORS and TLM.

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AUTHOR CONTRIBUTION

All authors contributed to the manuscript substantially and have agreed to the final submitted version.

DATA AVAILABILITY STATEMENT

Author elects to not share this data.

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