

ORIGINAL ARTICLE

Transoral laser microsurgery for oropharyngeal squamous cell carcinoma: A paradigm shift in therapeutic approach

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ABSTRACT: *Background.* The contemporary treatment of oropharyngeal squamous cell carcinoma (SCC) is an area of debate. We report outcomes of a minimally invasive approach involving transoral laser microsurgery (TLM).

Methods. A consecutive series of patients ($n = 153$) undergoing primary TLM for oropharyngeal SCC from 2006 to 2013 was studied. Human papillomavirus (HPV) status was determined by p16 immunohistochemistry and high-risk HPV DNA in situ hybridization. Survival analyses were evaluated using Kaplan–Meier statistics.

Results. Tumor subsites included tonsil ($n = 94$; 61.5%), tongue base ($n = 38$; 24.8%), and soft palate ($n = 21$; 13.7%), with the majority being American Joint Committee on Cancer (AJCC) stage III/IVa ($n = 124$; 81.0%) and HPV-positive ($n = 101$; 66.0%). Three-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS)

were 84.5%, 91.7%, and 78.2%, respectively. HPV-positivity portended favorable oncologic outcomes. One-year gastrostomy tube (G-tube) dependency was 1.3%.

Conclusion. To the best of our knowledge, this is the largest single-center TLM oropharyngeal SCC series to date. Our data suggest that TLM +/- postoperative radiotherapy (PORT) results in at least as good oncologic outcomes as chemoradiotherapy (CRT), while conferring swallowing function advantages. © 2016 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2016

KEY WORDS: carcinoma, squamous cell/surgery, oropharyngeal neoplasms/surgery, laser therapy/methods, oropharyngeal neoplasms/mortality, neoplasm recurrence, local, survival analysis

INTRODUCTION

Oropharyngeal squamous cell carcinoma (SCC) affecting the tonsils, tongue base, and/or soft palate, is a rapidly increasing disease in the United Kingdom and other developed countries, presumed to be a result of Human papillomavirus (HPV) infection; data suggest that, in areas of Europe, up to 70% of oropharyngeal SCCs are now HPV-associated.^{1–3} It is now widely accepted that HPV-driven oropharyngeal SCC represents a separate disease entity with distinct tumor biology to that of HPV-negative disease, with a propensity to affect younger patients, often in the absence of conventional risk factors,

while conferring favorable survival.^{1,4–7} Indeed, HPV status has been demonstrated to be a strong and independent prognostic factor for survival, with HPV-positive oropharyngeal SCC carrying a 58% reduction in the risk of death compared to HPV-negative oropharyngeal SCC (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.27–0.66).⁴

Despite the absence of level I evidence comparing surgical and nonsurgical approaches in the management of oropharyngeal SCC, cisplatin-based chemoradiotherapy (CRT) is generally considered the current standard of care for intermediate and advanced stage (American Joint Committee on Cancer [AJCC] stage III/IVa) oropharyngeal SCC in the majority of centers in the United Kingdom, Northern Europe, and the United States.^{1,8} This practice is largely predicated on the recognition of the significant morbidity associated with open surgical approaches and the enhanced survival noted with concurrent CRT over radiotherapy (RT) alone in the treatment

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of SCC of the head and neck (SCCHN) in general, and in particular of the larynx and oropharynx.^{1,9–16} However, the use of concurrent CRT or open surgery (involving mandibulotomy and reconstruction) followed by adjuvant RT for the treatment of oropharyngeal SCC results in significant long-term dysphagia.^{11,15–25} Therefore, as the survival outcomes resulting from surgical and nonsurgical strategies seem equitable, reducing the impact of treatment on long-term function is key in patients with oropharyngeal SCC, and in particular those with HPV-positive disease who have a favorable prognosis and tend to be younger and otherwise medically fit at presentation.⁴ Although treatment deintensification strategies in the HPV-positive patient population have been advocated — including reducing the total dose of radiation, addition of biotherapy, omission of chemotherapy, and/or surgical resection via a transoral approach^{2,9} — transoral surgery added to conventional treatments (eg, CRT) has also been advocated as a mechanism of intensifying treatment in patients with poorer prognosis oropharyngeal SCC.^{1,26} Accordingly, transoral laser microsurgery (TLM) as part of a deintensification strategy in HPV-positive oropharyngeal SCC is currently under investigation in the U.S.-based Eastern Cooperative Oncology Group-3311 (NCT01898494) and ADEPT (NCT01687413) and the U.K.-based PATHOS (NCT02215265) clinical trials. Concurrently, the role of TLM in treatment intensification of HPV-negative and clinicopathological high-risk HPV-positive oropharyngeal SCC is being investigated in the U.K.-based COMPARE clinical trial (UKCRN ID 18621).

TLM and transoral robotic surgery (TORS) are minimally invasive surgical techniques that are used to resect oropharyngeal SCC tumors with the aim of reducing long-term functional (particularly swallowing) deficit. At Aintree University Hospitals NHS Foundation Trust, Liverpool, United Kingdom, the largest centralized head and neck cancer unit in the United Kingdom, it has been routine practice to offer primary TLM for oropharyngeal SCC since 2006. The purpose of this study, which constitutes the largest consecutive single center series published to date, is to present the oncologic and functional outcomes and our experience of this approach, and to attempt to define its role in future treatment strategies for oropharyngeal SCC.

PATIENTS AND METHODS

Patients and setting

This was a retrospective analysis of consecutive patients with oropharyngeal SCC treated with TLM from July 2006 to April 2013 at Aintree University Hospitals. Patients were identified from our regional head and neck cancer database and cross-referenced with theater records. The study cohort was restricted to patients with at least 12 months' follow-up data who were treated with curative intent using TLM as their primary treatment modality, combined with postoperative adjuvant therapy when appropriate.

All clinicopathological, treatment, and oncologic and functional outcome data for eligible patients were extracted from hospital records. HPV status was determined from pathological resection specimens using p16

immunohistochemistry (CINtec Histology, Roche MTM Laboratories, Basel, Switzerland), followed by high-risk HPV DNA in situ hybridization (INFORM HPV III Family 16 probe B; Ventana Medical Systems, Tucson, AZ), as previously described.²⁷

Operative technique and adjuvant therapy

Tumor resections were performed under microscopic control and using an array of equipment, including bivalved adjustable laryngoscopes (Karl Storz, Tuttlingen, Germany) as well as a Boyle–Davis tonsil gag or FK-WO TORS laryngopharyngoscope (Olympus Medical Systems, Hanoi, Vietnam), to facilitate transoral tumor exposure. Resection was undertaken using an AcuPulse 40WG CO₂ laser (Lumenis, Elstree, UK), with the laser beam directed using an AcuSpot 712 micromanipulator (Lumenis) attached to the operating microscope. Continuous superpulse was the laser setting of choice and power settings varied from 2 to 10 W depending on the individual case.

In order to maximize appreciation of 3D orientation, tumors were resected in a transtumoral manner, as popularized by Steiner and Ambrosch,²⁸ and subsequently pinned and orientated on a corkboard to facilitate accurate histopathological reporting of surgical resection. Excision was assessed pathologically by measuring tumor relationship to the deep and mucosal surfaces of the primary tumor specimen, as well as examining a series of marginal biopsies taken from the tumor bed and periphery after perioperative microscopic tumor clearance. A zero-tolerance policy for involved marginal biopsies was used and subsequent procedures were undertaken in all cases if the marginal biopsies were reported as positive to ensure complete clearance of disease. In such cases, intraoperative frozen sections were utilized as required, particularly during base of tongue (BOT) resections in which intraoperative microscopic evaluation of tumor resection tends to be more challenging.

Elective or therapeutic neck dissections, the indication and extent of which was based on standard oncological criteria, were performed in a standard fashion and in a single surgical session either preceding or after TLM. Unless clinically indicated, neck dissection did not include level I nodes. Additionally, after 2 cases of fatal hemorrhage (see surgical complications below) it became our standard practice since September 2010 to ligate the ipsilateral external carotid artery (ECA), or branches thereof, cranial to the superior thyroid artery, in order to mitigate the risk of hemorrhage from the primary tumor resection site.

Decisions to administer adjuvant therapy were made at a multidisciplinary level, and were based primarily on pathology reports of TNM stage and, in particular, the number of involved ipsilateral and/or contralateral cervical lymph nodes, the presence of extracapsular spread (ECS) from nodal metastasis, as well as patient functional status and comorbidity. In our practice, as previously stated, there is a zero-tolerance for positive surgical marginal biopsies. In this context, in keeping with the principles of TLM, tumor extending to the main section resection margin is not considered as a positive resection margin and therefore is not generally taken into account when considering the advisability or nature of adjuvant

treatment. Similarly, in our practice, the presence of ECS did not automatically result in the prescription of postoperative CRT. Only when ECS amounting to a soft tissue deposit²⁹ was present or ECS was associated with other pathological features of adverse outcome (eg, perineural and/or vascular invasion, multiple lymph nodes node exhibiting ECS), was postoperative CRT prescribed for patients considered fit enough.

For lateralized carcinomas, RT was delivered using standard 3D conformal RT to a dose of 63 Gy in 30 fractions. For nonlateralized tumors in the earlier part of the study, RT was delivered using 3D conformal RT with matched posterior neck electrons, if required, to a dose of 64 Gy in 32 fractions ($n = 20$). In the later years of the study, parotid-sparing intensity-modulated RT (IMRT) to a dose of 63 Gy in 30 fractions was universally used. When postoperative CRT was given, the RT dose was 66 Gy in 33 fractions, with concurrent cisplatin administered at 100 mg/m² on days 1, 22, and 43 of the RT regimen. In all cases, the uninvolved lower neck was treated by matched anterior field (unilateral or bilateral, as appropriate), with central shielding of the larynx, pharynx, upper esophagus, and spinal cord to a dose of 40.5 Gy in 15 fractions.

Statistical analysis

IBM SPSS version 21 (Armonk, NY) was used for statistical analyses. Time-to-event analyses using Kaplan–Meier statistics were used to estimate locoregional control, overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS). All survival/recurrence times were calculated from the date of treatment completion to the date of occurrence of the event or the date of last follow-up. In cases in which the follow-up extended beyond 60 months and no event of interest had occurred, patients were censored at 60 months. Tumor recurrence was defined as the emergence of further disease at least 6 months after complete TLM resection.

Log-rank statistics were used to examine the relationship and determine statistical significance ($p \leq .05$) among OS, DSS, DFS and the following variables: AJCC stage, presence of ECS for those patients who had undergone neck dissections, HPV status, and tumor subsite (tonsil vs BOT). To calculate Hazard Ratios (HR) to quantify effect size, Cox proportional hazards models were fitted where appropriate.

Ethical considerations

Data and tissue collection and analysis for this study was undertaken in accordance with previously granted ethical approval from North West 5 Research Ethics Committee (Ref: 10/H1010/37). All patient data were kept anonymous and encrypted throughout.

RESULTS

Clinicopathological and treatment details

One hundred fifty-three consecutive patients were eligible for inclusion in this study, 64 and 89 of whom were treated before and after our ECA ligation strategy, respectively. Mean patient age was 59 years (range, 28–81

TABLE 1. Clinicopathological and treatment details for all patients.

Characteristic	No. of patients (%)
Tumor subsite	
Tonsil	94 (61.5)
BOT	38 (24.8)
Soft palate	21 (13.7)
HPV status	
Positive	101 (66.0)
Negative	52 (44.0)
AJCC stage	
I	13 (8.5)
II	16 (10.5)
III	38 (24.8)
IV	86 (56.2)
T classification	
T1	42 (27.5)
T2	74 (48.4)
T3	37 (24.2)
N classification*	
N0	31 (20.3)
N1	27 (17.6)
N2	94 (61.4)
N3	1 (0.7)
Neck dissection	
Yes	123 (80.4)
No	30 (19.6)
ECS [†]	
Yes	50 (40.7)
No	73 (59.3)
Adjuvant treatment	
None	24 (15.7)
RT alone	121 (79.1)
CRT	8 (5.2)

Abbreviations: BOT, base of tongue; HPV, human papillomavirus; AJCC, American Joint Committee on Cancer; ECS, extracapsular spread; RT, radiotherapy; CRT, chemoradiotherapy.

* In cases in which no neck dissection was undertaken, the cN is detailed rather than the pN.

[†] Percentages quoted for ECS are with respect to the number of patients who underwent neck dissections and consequently for which a pN status and pathology report was available.

years) and 71.9% of patients were men (110 of 153). Mean duration of follow-up for all surviving patients in the study cohort was 40 months (range, 12–95 months). Additional clinicopathological and treatment details are summarized in Table 1. Of particular note, 66% of patients (101 of 153) presented with HPV-positive tumors.

Surgical complications

Major postoperative bleeding occurred in 4 cases (2.6%) at postoperative days 2, 4, 5, and 8. In 2 cases, return to the operating theater for endoscopic arrest of hemorrhage was successful, but, regrettably, in the other 2 cases, hemorrhage proved fatal. It was after these episodes that we changed our practice, as described above, to routinely ligate the ECA, or branches thereof, after neck dissection. Since that change in practice, no episodes of major hemorrhage have occurred. Otherwise, complications relating directly to TLM were minor and included pain at the primary site, bruising to the lips, alveolus, and tongue. In all cases, such complications were successfully managed conservatively and resulted in no long-term adverse sequelae.

TABLE 2. Patterns of recurrence with respect to primary disease American Joint Committee on Cancer stage.

AJCC stage	Local	Regional	Distant
I	2	1	0
II	1	0	0
III	4	4	1
IV	5	3	3

Abbreviation: AJCC, American Joint Committee on Cancer.

Oncologic outcomes

Sixteen patients (10.4%) suffered disease recurrence during the study period at a mean time of 16 months (range, 6–36 months) after completion of initial treatment. Of these cases, recurrence occurred at more than 1 site in 4 patients. Patterns of recurrence with respect to primary disease stage are illustrated in Table 2. Twelve patients (7.8%) suffered local and/or regional recurrence, resulting in a 3-year locoregional control estimate of 89.6% (see Figure 1).

One hundred twenty-six patients (82.4%) were living without evidence of disease recurrence, or further recurrence in cases of successful salvage, at most recent follow-up or at completion of 60 months' follow-up. Fourteen patients (9.2%) died of causes related to their oropharyngeal SCC, 11 (7.2%) died of intercurrent diseases, and 2 (1.3%) died of second primary tumors. Three-year OS, DSS, and DFS were 84.5%, 91.7%, and 78.2%, respectively (see Figure 2).

HPV status was the only variable observed to impact significantly on any survival parameter with no statistically significant influence noted for AJCC stage, ECS, or tumor subsite (Table 3). Specifically, HPV positivity was associated with favorable OS (HR, 0.286; 95% CI, 0.128–

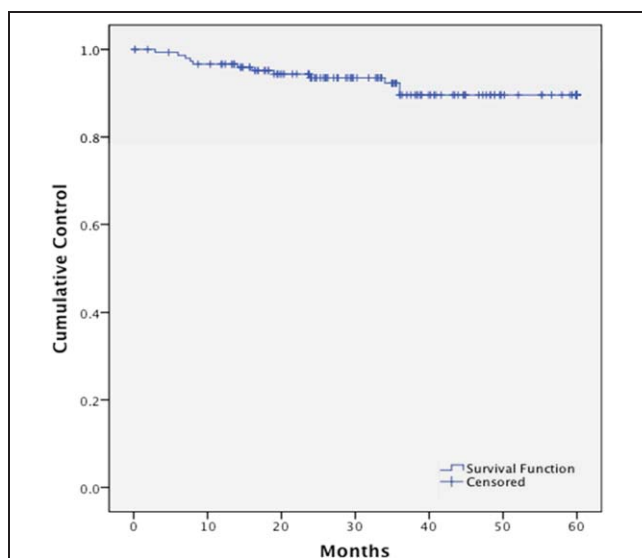


FIGURE 1. Kaplan–Meier plot of locoregional disease control for entire study cohort (3-year estimate 89.6%). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

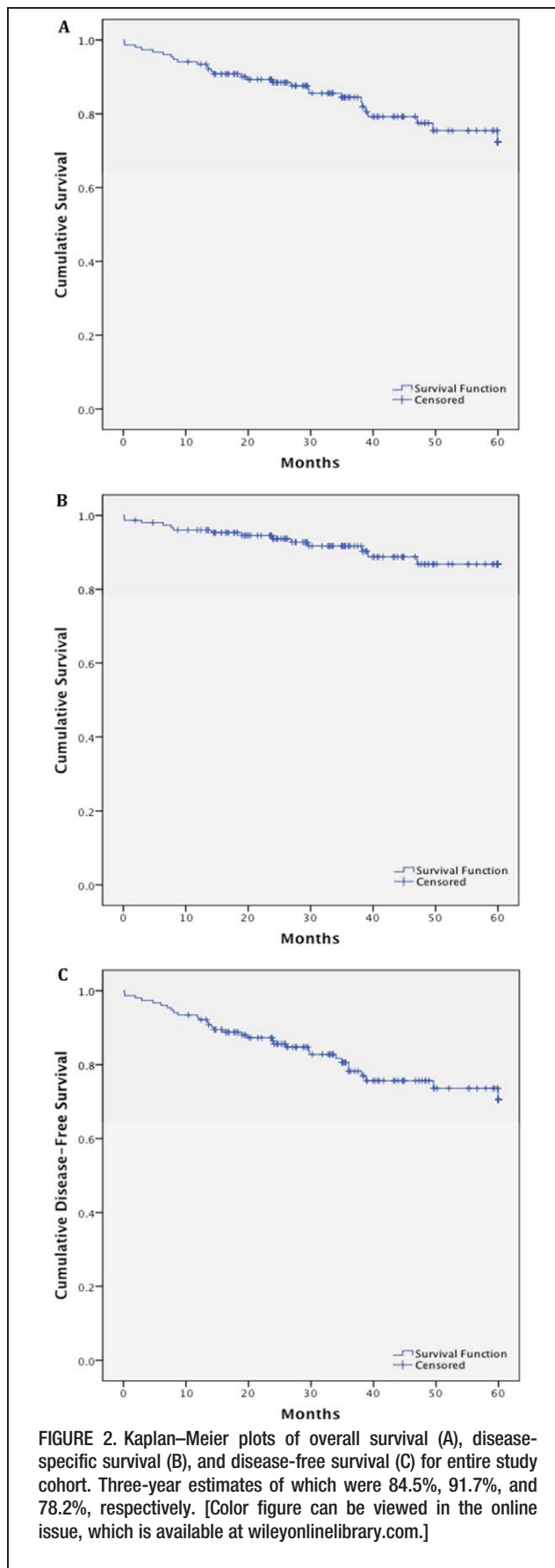


FIGURE 2. Kaplan–Meier plots of overall survival (A), disease-specific survival (B), and disease-free survival (C) for entire study cohort. Three-year estimates of which were 84.5%, 91.7%, and 78.2%, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 3. Univariate analysis of the impact of different variables on survival outcome measures as assessed using log-rank tests.

Variables	OS	DSS	DFS
AJCC stage	$p = .385$	$p = .488$	$p = .079$
ECS	$p = .271$	$p = .431$	$p = .271$
HPV status	$p = .001^*$	$p = .304$	$p < .0001^*$
Tumor subsite [†]	$p = .578$	$p = .345$	$p = .697$

Abbreviations: AJCC, American Joint Committee on Cancer; ECS, extracapsular spread; HPV, human papillomavirus.

* These figures indicate statistical significance ($p < .05$).

[†] Analysis for tumor subsite done for only the two most frequently implicated subsites (tonsil and base of tongue), with the small number of soft palate cases ($n = 21$) excluded.

0.640) and DFS (HR, 0.234; 95% CI, 0.108–0.510), as depicted in Figure 3.

Within the HPV-positive subgroup, again, no significant relationships were observed between any survival parameter and either AJCC stage or ECS.

Functional outcomes and bed occupancy

All patients were assessed with regard to their swallowing function by a dedicated speech and language therapist during their postoperative inpatient stay. In no cases were gastrostomy (G-tubes) inserted pretreatment. One hundred forty-nine patients (97.4%) were swallowing normally on discharge from the hospital, with the remaining 4 patients discharged on G-tube feeding. Of those requiring G-tube feeding on discharge, in 2 cases, the G-tubes were removed at 2 and 4 months after discharge subsequent to regained swallowing function, whereas in 2 cases, G-tubes remain in situ. As such, the 1-year G-tube dependency rate for our patient group was 1.3%.

As was more common in our early experience, 12 patients underwent elective tracheostomy, performed at the time of TLM. In 1 case, this was undertaken to protect the airway after exposure of the internal carotid artery during primary tumor resection, whereas, in the remainder of cases, the decision to perform a tracheostomy was taken preoperatively, in light of the presenting tumor volume and anticipated airway/aspiration-related complications. All patients who underwent tracheostomy were decannulated successfully in the postoperative period at a mean of 10 days (range, 4–15 days). Since adopting our ECA ligation strategy, only 1 patient had an elective tracheostomy with respect to anticipated postoperative aspiration/airway compromise.

For the whole cohort, the mean duration of postoperative inpatient stay after TLM was 8 days (range, 0–41 days). Two patients remained in the hospital for protracted periods (24 and 27 days) owing to swallowing issues, whereas in 4 cases prolonged admission was attributable to comorbidities and social issues. Otherwise, all patients were discharged within 10 days of surgery. However, after commencement of our ECA ligation strategy, the inpatient stay was reduced to a mean of 5 days (range, 1–27 days) as protracted monitoring for hemorrhage was no longer required. Furthermore, when adjusted to account only for reasons attributable to oropharyngeal SCC treatment (ie, excluding, for example, social reasons

for delayed discharge), the inpatient stay was reduced to a mean of 3 days.

DISCUSSION

The present study, which represents the largest single-center experience of the use of TLM as a primary treatment modality for oropharyngeal SCC, supports the notion that primary TLM is an oncologically sound therapeutic option for oropharyngeal SCC. For our study cohort as a whole, 81.0% of which comprised stage III or IV disease, we observed a 3-year locoregional control rate of 89.6% and, respective, 3-year OS, DSS, and DFS rates of 84.5%, 91.7%, and 78.2%, which, although challenging to compare with the oncologic outcomes from previous contemporary surgical series owing to varying

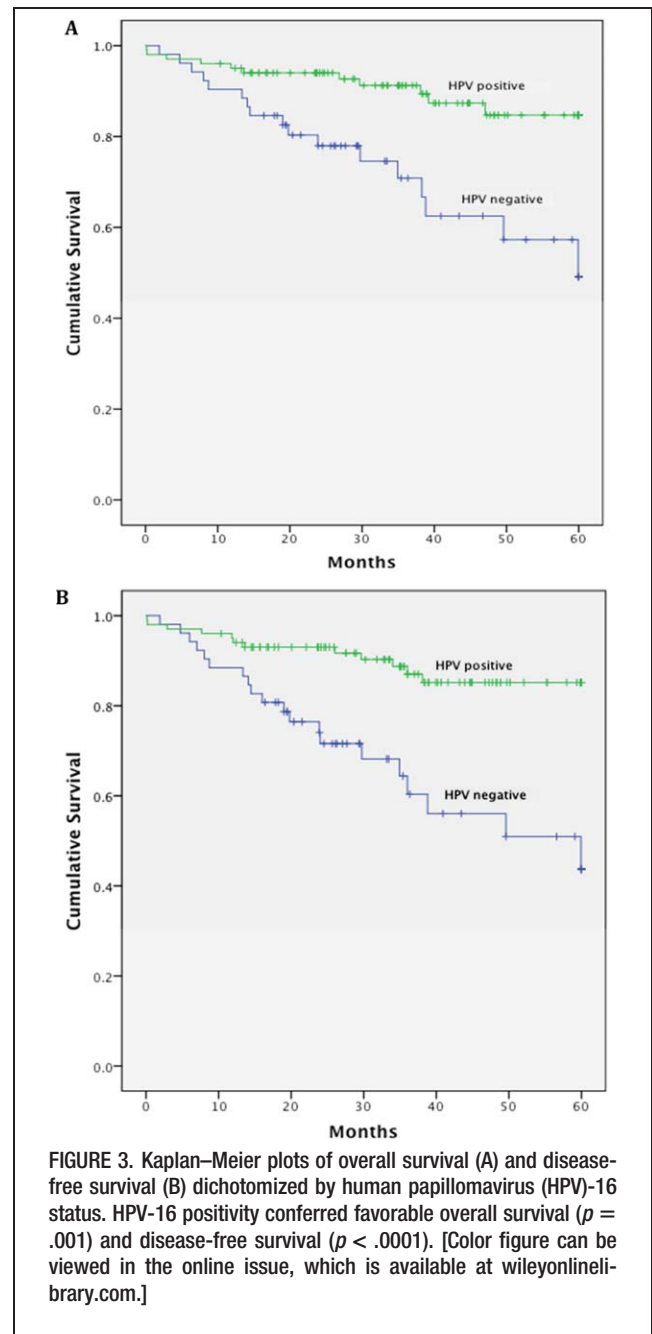


FIGURE 3. Kaplan-Meier plots of overall survival (A) and disease-free survival (B) dichotomized by human papillomavirus (HPV)-16 status. HPV-16 positivity conferred favorable overall survival ($p = .001$) and disease-free survival ($p < .0001$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

distributions of disease stage, HPV status, and adjuvant therapy strategy, seem broadly consistent. In the earliest published report of primary TLM to treat oropharyngeal SCC, Steiner et al³⁰ noted a 5-year local control estimate of 85% and DFS and OS estimates of 73% and 52%, respectively, for a small cohort ($n = 48$) of patients with BOT SCC, whereas a recent update of these data, including an additional 82 patients with more mature follow-up, demonstrated respective 5-year local control, DFS, and OS rates of 84%, 69%, and 59%.³¹ Similar oncologic outcomes have been reported in three US single-center series,^{13,32,33} with particularly propitious results reported in a recent appraisal of 80 patients with advanced oropharyngeal SCC, albeit predominantly low T classification, from the Mayo Clinic Arizona: respective 3-year locoregional control, DFS, and OS estimates were 98.6%, 91.1%, and 93.7%, respectively.³² Perhaps most notably, however, in the largest TLM oropharyngeal SCC study to date – a multicenter series that amalgamated data for 204 patients followed for a minimum of 2 years from the 3 aforementioned U.S. centers – respective 2-year and 5-year estimates of OS, DSS, and DFS were reported as follows: 89% and 78%, 91% and 84%, and 85% and 74%.⁹ Furthermore, oncologic outcomes reported for oropharyngeal SCC treated with TORS, which follows broadly the same surgical and oncologic principals as TLM, have also been congruous.³⁴

Importantly, oncologic results achieved with such minimally invasive surgical approaches are at least comparable to those reported for primary nonsurgical regimens. Again, although comparison is hindered by differences between studies in disease stage and reporting of positivity for HPV status, those that are comparable, at least in terms of disease stage and which have been conducted during the era of high prevalence HPV-driven disease, reveal very similar oncologic outcomes. In a CRT study of 71 patients all with AJCC stage III/IVa oropharyngeal SCC, and containing 32% T3 and T4 cases, Huang et al¹² reported 3-year OS and locoregional control rates of 83% and 90%, respectively (salvage surgery included). In contrast, 3-year OS and DFS estimates in the oropharyngeal SCC subgroup ($n = 433$; 100% AJCC stage III/IVa) of the Radiation Therapy Oncology Group 0129 study comparing accelerated-fractionation RT and standard-fractionation RT as part of primary CRT regimens were 82.4% and 73.7% for HPV-positive patients and 57.1% and 43.4% in HPV-negative patients, respectively.⁴ More recently, Setton et al³⁵ reported a 3-year OS of 84.9% and respective local and regional failure rates of 5.4% and 5.6% in the largest primary nonsurgical oropharyngeal SCC series to date, which included 442 patients (94% AJCC stage III/IV) all treated with IMRT, of which 88% received concurrent chemotherapy. Proponents of primary CRT would argue for the systemic benefits of CRT over surgery or RT alone in reducing recurrences and deaths from distant metastases, as has been reported in earlier clinical trials in SCCHN more generally.³⁶ It is, however, likely that some degree of discrepancy existed among patient groups in these trials regarding their pretreatment distant metastatic status in view of the fact that whole body functional imaging techniques were not available for routine use, thereby introducing bias in compar-

ing treatment groups.³⁶ Furthermore, in the present study, in which only 8 patients (5.2%) received adjuvant CRT, only 2.6% of all patients suffered distant recurrences, whereas 5.9% did so in the TLM multicenter series, in which 16.2% were treated with adjuvant CRT,⁹ outcomes comparable to the primary CRT series.

Functional outcome, most notably posttreatment swallowing function, is also crucial when considering treatment options for patients with oropharyngeal SCC, particularly given the apparently similar oncologic results achieved with competing therapeutic approaches. Indeed, the belief that “organ-preserving” primary nonsurgical treatment regimens offered favorable functional outcomes in comparison with traditional en bloc surgical approaches was a principal motivating factor in the widespread shift toward primary nonsurgical management of SCCHN, oropharyngeal SCC included.^{8,37} Although there is no doubt that previous major open surgical approaches carried significant risks of posttreatment morbidity and mortality, it is now apparent that use of chemotherapy in conjunction with RT to the head and neck is also associated with high rates of acute and late toxicity in the majority of patients, particularly with respect to deglutition, over and above those seen with RT alone.^{11,15–25} Although, when assessing swallowing function there is no universally recognized single method of measuring outcome,³⁸ it is apparent that primary CRT regimens often necessitate protracted or permanent nonoral feeding, with high rates of G-tube dependency reported – a crude but objective measure of swallowing outcome. Indeed, in an analysis of swallowing outcomes after definitive CRT for advanced oropharyngeal SCC, Shiley et al²¹ observed a 1-year G-tube dependency rate of 31%, whereas Patterson et al²² noted a similarly high rate in a prospective longitudinal study of swallowing outcomes in a cohort of patients with advanced SCCHN treated with CRT, a significant proportion of whom were treated for oropharyngeal SCC (53%). Although the use of IMRT certainly seems to have improved the situation, for example, a recent large-scale U.S. multi-institution pooled analysis demonstrated a 1-year dependence of 8.6% in those treated with concurrent chemotherapy and IMRT ($n = 1238$),³⁹ results from our experience with TLM remain favorable by comparison (1-year G-tube dependency of 1.3%). Moreover, similarly low rates of G-tube dependency have been reported in the other aforementioned TLM series.^{13,32,33} Unfortunately, although such favorable G-tube dependency rates are compelling, our series, and indeed the previous TLM series, lack more comprehensive data regarding swallowing function pretreatment and posttreatment, and, more importantly, lack a direct comparator group treated nonsurgically to allow for a more robust analysis of swallowing outcomes. To this end, there is an ongoing effort in our department to incorporate routine measurement of an array of both subjective and objective swallowing evaluations as part of our standard minimum dataset. Nonetheless, a number of recent direct comparator studies specifically examining swallowing outcomes have also demonstrated advantageous swallowing outcomes in those treated with minimally invasive surgery compared to a primary nonsurgical approach.^{40,41} In a nonrandomized, case-matched study of patients

treated for advanced oropharyngeal SCC with either CRT or TLM, O'Hara et al⁴⁰ observed significantly better swallowing scores for the TLM cohort at 3 months after treatment, as assessed with patient-reported outcomes using the MD Anderson Dysphagia Inventory, clinician-rated dietary texture restrictions using the Normalcy of Diet scale, and objective swallow performance using the timed Water Swallow Test. Furthermore, all patients in the TLM cohort were able to complete the Water Swallow Test, whereas, in the CRT group, 5 patients were unable to do so owing to overt aspiration.⁴⁰ Similarly, in a recent prospective longitudinal study examining patient-rated swallowing function in patients with advanced oropharyngeal SCC treated either with TORS or CRT, MD Anderson Dysphagia Inventory scores were significantly more favorable for those treated with TORS at 6-month and 12-month follow-up.⁴¹

This question of survivorship becomes yet more pertinent when considering the ever-increasingly prevalence of HPV-positive oropharyngeal SCC. HPV-driven disease is associated with excellent long-term oncologic outcomes irrespective of treatment modality used,^{1,4-8,42} something also observed incontrovertibly in our study group, with HPV positivity conferring a 76.6% reduction in risk of death and/or disease recurrence. Additionally, HPV-driven disease tends to affect younger and generally medically fitter patients without conventional risk factors, who are thus likely to experience the functional ramifications of their treatment long term. Consequently, it has been argued that treatment strategies for such patients should be deintensified in order to optimize the therapeutic index,^{1,8} but uncertainty remains regarding the optimum means by which to accomplish this. Upfront minimally invasive endoscopic surgical techniques, however, lend themselves well to this strategy: primary tumors can be resected with little, if any, functional deficit, and although the functional advantage may be obviated to a degree with administration of adjuvant therapy, this can be tailored based on the full pathological and staging assessment made available by surgical resection, notionally enabling reduced doses of adjuvant RT, potential reduction in RT fields, and rationalization of chemotherapy use. The current evidence for use of CRT in the postoperative setting comes from 2 seminal trials from 2004, which demonstrated significant improvements in survival and locoregional control for patients with advanced SCCHN treated with postoperative CRT compared with postoperative RT (PORT) only.^{15,18} A subsequent pooled analysis of these studies demonstrated that postoperative CRT significantly improved survival in patients with microscopically involved surgical resection margins and/or ECS, and, on this basis, postoperative CRT became the standard of care for the adjuvant treatment of patients with head and neck cancer with these high-risk pathological features.¹⁶ These studies, however, included all subsites of SCCHN and, given the chronology of patient recruitment to these trials, during which time the incidence of HPV-positive oropharyngeal SCC was in the region of 35.3% (95% CI, 27.8–43.5%),² it is likely that HPV-positive oropharyngeal SCC was not well-represented. Accounting for these factors, only 28 to 44 and 50 to 76 patients, respectively, in these trials,

would have had HPV-positive oropharyngeal SCC, and, as such, the apparent benefit of postoperative CRT may not extrapolate to the postoperative management of HPV-positive oropharyngeal SCC. Indeed, results from the present study lend credence to this notion: in our HPV-prevalent patient group (66.0% of our cases) excellent oncologic outcomes were achieved despite the overwhelming majority of our study cohort (94.8%) being treated without the use of postoperative CRT even in the presence of ECS in a considerable proportion of patients (44.4% of those who underwent neck dissections), whereas ECS was not predictive of oncologic outcome. Congruous results have also been observed in previous TLM series with similarly high rates of HPV positivity in which only a minority of patients were treated with adjuvant CRT,^{9,13,30-33} albeit a greater proportion than in the present series. Furthermore, in the U.S. multicenter TLM study, again, ECS was not prognostic and no significant survival advantage was observed in the subgroup of patients receiving postoperative CRT compared with those who received PORT.⁹ These findings were corroborated in a follow-up study by the same research group using multivariate and matched analyses controlling for conventional high-risk pathological criteria in a patient cohort with HPV-positive disease exclusively.⁴³ Although such findings underpin the shift toward reduced intensity adjuvant treatment strategies, it is hoped that the U.S.-based ADEPT and Eastern Cooperative Oncology Group 3311 randomized controlled trials (RCTs), as well as the U.K.-based RCT, PATHOS trial designed to truly, and more definitively, address these issues will help inform future management strategies for surgically treated HPV-positive oropharyngeal SCC.

CONCLUSIONS

Outcomes from this study, in conjunction with the limited volume of previously published data, attest primary TLM – in combination with PORT when indicated – for the treatment of intermediate stage oropharyngeal SCC to be at least as oncologically effective as current nonsurgical treatment regimes, while conferring discernible functional advantages with respect to swallowing. Such findings substantiate TLM as a highly effective primary treatment option for the management of selected cases of oropharyngeal SCC. Our data also lend support to the notion of treatment deescalation for HPV-positive oropharyngeal SCC, and, once again, invites scrutiny of the need for postoperative CRT for pathologically high-risk cases of HPV-positive oropharyngeal SCC. The authors accept, however, that the conclusions that can be drawn from this study are limited because of its retrospective nature and the lack of robust experimental design, namely, the absence of comparator groups. Nonetheless, we believe that the evidence presented is sufficient to consider primary TLM as a putative standard of care and validates the necessity to perform appropriately powered RCTs to identify the optimal treatment strategies for both clinicopathological low-risk HPV-positive as well as clinicopathological high-risk HPV-positive and HPV-negative oropharyngeal SCC subgroups.

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