Transoral laser microsurgery ± adjuvant therapy versus chemoradiotherapy for stage III and IVA oropharyngeal squamous cell carcinoma: Preliminary comparison of early swallowing outcomes

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ABSTRACT: Background. Observational data suggests transoral surgery may offer benefit in swallowing over chemoradiotherapy. Methods. In this preliminary, non-randomized study, patients with stage III and IVA oropharyngeal carcinoma treated with transoral laser microsurgery (TLM) were assessed pretreatment and 3 months after treatment using the MD Anderson Dysphagia Inventory (MDADI), the Performance Status Scale (PSS), and a timed Water Swallow Test (WST). Comparisons were made with a historical chemoradiotherapy (CRT) cohort. Results. Based on patients with measurements at both times, the decrease in score between baseline and 3 months was greater for CRT patients (n = 26–28) than for TLM (n = 20–21) patients for each of MDADI, PSS, and WST. A repeated measures analysis that looked at all 3 scores simultaneously and allowed for missing values gave mostly similar results (except for MDADI). Conclusion. TLM was associated with good early swallowing outcomes at 3 months and may offer a benefit over CRT. The results should be viewed as preliminary data, providing useful reference for any proposed controlled trial. © 2015 Wiley Periodicals, Inc. Head Neck 37: 1488–1494, 2015

KEY WORDS: oropharyngeal squamous cell carcinoma, transoral surgery, chemoradiotherapy, swallowing

INTRODUCTION
The management of oropharyngeal squamous cell carcinoma (SCC) is a hotly debated topic. The increased survival noted with concurrent chemoradiotherapy (CRT), over radiotherapy (RT) alone, along with the recognition that traditional open surgical approaches were associated with greater morbidity1 led to an ever increasing trend toward primary nonsurgical treatment for these patients. However, the realization that CRT is associated with greater long-term morbidity than RT alone, the popularization of transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) and the recognition of a distinct population of patients with oropharyngeal SCC caused by human papillomavirus (HPV), has rekindled the debate. The incidence of HPV-positive oropharyngeal SCC now outweighs that of HPV-negative disease in some areas of the world. The prognosis from HPV-positive oropharyngeal SCC is better than HPV-negative disease and the survival after treatment seems roughly similar when taken from distinct nonsurgical and surgical trials.2,3

With the improved prognosis for HPV-positive oropharyngeal SCC patients has come the question of survivorship. These patients tend to be younger, generally medically fit, nonsmokers, and are employed. Swallowing is a top priority concern for head and neck cancer survivors.4 Furthermore, younger patients report more severe swallowing difficulties than older patients.4 Although the issue of posttreatment function is clearly of huge importance, the literature does not allow a straightforward assessment of the outcomes after different treatment options.

How can we maximize functional outcome while maintaining survival prognosis? Advocates of TLM and TORS claim that swallowing is improved with these methods; patients with low volume disease (T1 and T2), N0 or N1 neck disease, clear surgical margins, and no extracapsular spread (ECS) are candidates for single modality surgery. However, this group of patients forms roughly 25% of patients with oropharyngeal SCC and would be candidates for RT alone rather than CRT. Surgery allows accurate staging of the disease, enabling reduced doses of adjuvant RT, with or without chemotherapy, and potential reduction in the RT fields, particularly for lateralized oropharyngeal SCC tumors. Advocates of CRT cite the greater...
level of evidence in support of its survival efficacy and the potential benefits of intensity modulated radiotherapy (IMRT), although there is no published research directly comparing swallowing outcomes for IMRT and conventional CRT. In mixed treatment groups, larger radiation fields, accelerated fractionation, and the addition of chemotheraphy were associated with worse swallowing.5–7

Following a number of patients who suffered particularly severe functional morbidity after primary CRT, with negligible improvement in the first year after treatment,8 this unit opted to move to offer primary TLM for patients with oropharyngeal SCC. The initial purpose of this study was to analyze swallowing outcomes in both TLM and CRT groups. However, analysis revealed that very few patients with surgically appropriate disease received CRT and, over the period in question, primary CRT was mainly given to T4 tumors. Early swallowing function after TLM has therefore been compared with a historic cohort of stage-matched patients undergoing nonsurgical treatment and who received the same prospective swallowing evaluation.

The primary purpose of this preliminary, non-randomized study was to assess the change in early swallowing function from baseline to 3 months after treatment between the TLM and historical CRT groups. Specifically, patients with stage III and IVA disease have been included. These stages represent tumors that merit treatment with CRT and are resectable via TLM surgery. Previous work indicates that, although some improvement in swallowing does occur after 3 months, the improvement is small. Longitudinal studies have shown that swallowing at 3 months is a very strong indicator of likely long-term function.5,6,8

MATERIALS AND METHODS

Patients presenting to the Sunderland Royal Hospital Head and Neck Multidisciplinary Team meeting with primary resectable stage III and IVA SCC of the oropharynx from August 2011 until March 2013 were treated with TLM surgery and adjuvant therapy. This was not a trial of the technique, but more a change in policy by the team away from CRT. All patients undergoing TLM were included in a prospectively collected database. Swallowing is a multidimensional construct, and assessments from different domains can give differing results. Therefore, 3 outcomes were collected: a swallowing questionnaire, a clinician-rated dietary texture scale, and a timed water swallow test, as detailed below. Data were collected at baseline, which will have occurred shortly after diagnostic biopsies, and at 3 months after completion of all therapy. Functional outcomes were then compared against a historical nonsurgical case series recruited for a previous study.5 All patients with stage III and IVA disease of the oropharynx were extracted from this research database. These included some patients receiving RT alone, for various reasons. Routine HPV testing was only performed for the TLM group, comprising p16 immunohistochemistry and, when this was positive, in situ hybridization for high-risk HPV.10

Treatment by transoral laser microsurgery

Surgical resection of the primary tumor was performed as previously described in the literature.11 The FK retrac-
performed if the patient reported choking on fluids and was scored as a zero. The test has good reliability and validity and is sensitive to measuring change over time and differentiating between treatment outcomes.\textsuperscript{8,16,17}

**Statistical analysis**

Both parametric (repeated measures) and nonparametric analyses were performed to compare the change in swallowing scores between baseline and 3-month follow-up between the 2 groups (TLM and CRT). The multivariate repeated measures analysis, conducted using the GLM Repeated Measures option in SPSS, looked at changes in all 3 scores simultaneously and adjusted for missing values via multiple imputation, allowing for the fact that all scores lie between 0 and 100. This analysis was based on the assumption that the scores are normally distributed. However, because of the construction of the MDADI and PSS questionnaires, the assumption of normality is questionable; for instance, a difference of 10 on the MDADI score between 90 and 80 may not compare to the clinical difference of 10 between 50 and 40 on the same scale. Furthermore, as highlighted below, the scores have skewed distributions. Consequently, when considering each score in turn, Mann–Whitney \( U \) tests were used to look for differences in the change in score between groups, based on those patients with measurements at both baseline and 3 months. Particular attention was given to \( p \) values <.05. Analyses were performed using SPSS version 19.

**Ethical considerations**

Formal local research ethics committee approval was obtained for the original CRT group. Subsequently, the collection of the 3 swallowing outcomes has become routine practice in this department. Approval was obtained from the Sunderland Royal Hospital clinical governance department to collect the data.

**RESULTS**

Twenty-three patients treated with TLM and 33 patients treated with primary nonsurgical management, with complete demographic and tumor staging data, were included in the analysis. Every consecutive patient undergoing TLM within the study timeframe has been included in the descriptive results. Ninety-four percent of patients in the historical nonsurgical cohort agreed to take part in the data collection. Twenty-nine patients of the nonsurgical group were treated with primary nonsurgical management, with complete demographic and tumor staging data, were included in this calculation, there was a significant difference in baseline scores between the 2 groups for MDADI scores \((p = .078)\), PSS Normalcy of Diet \((p = .51)\), or WST \((p = .55)\). However, when all patients (including those with missing data) were included in this calculation, there was a significant difference in baseline scores on the MDADI between the 2 groups \((p = .012)\), but less evidence of a difference for PSS Normalcy of Diet \((p = .082)\) and no evidence of a difference for WST \((p = .43)\).

There were a higher proportion of T3 primary tumors in the CRT group \((13 \text{ of } 33)\) than the TLM group \((5 \text{ of } 23)\). When T3 tumors were removed from the descriptive analysis, the CRT group had mean pretreatment and

| TABLE 1. Patient demographics. |
|-------------------------------|
| Demographic                  | TLM \((n = 23)\) | CRT \((n = 33)\) |
| Mean age (SD)                | 59.3 (8.6)      | 59.3 (8.6)      |
| Sex                          |                 |                 |
| Male                         | 17              | 26              |
| Female                       | 6               | 7               |
| Site of tumor                |                 |                 |
| Tonsil                       | 15              | 18              |
| Base of tongue               | 7               | 11              |
| Posterior pharyngeal wall    | 1               | 2               |
| Soft palate                  | 0               | 2               |
| Overall stage                |                 |                 |
| III                          | 5               | 13              |
| IVA                          | 18              | 20              |
| T Classification             |                 |                 |
| N Classification             |                 |                 |
| T1                            | \((n = 5)\)     | \((n = 5)\)     |
| N1                            | 2               | 7               |
| N2                            | 1               | 2               |
| N2a                           | 9               |                 |
| N2b                           |                 |                 |
| N2a                           | 1               | 2               |
| N2b                           | 2               | 7               |
| N2                            |                 |                 |
| N1                            | 1               | 4               |
| N0                            | 2               | 2               |
| T2                            | \((n = 13)\)    | \((n = 15)\)    |
| T3                            | \((n = 5)\)     | \((n = 13)\)    |
| N0                            | 1               | 4               |
| N1                            | 1               | 7               |
| N2                            |                 |                 |
| Abbreviations: TLM, transoral laser microsurgery; CRT, chemoradiotherapy. |
3-month scores of 79.1 and 59.1 (MDADI), 76.4 and 36.0 (PSS Normalcy of Diet), and 17.3 and 13.0 (WST). Relative to the entire CRT group, mean scores for T1 to 2 tumors were slightly lower in the case of MDADI and PSS Normalcy of Diet and slightly higher in the case of WST.

Based on MDADI, 76% of the TLM group (16 of 21) and 92% of the CRT group (24 of 26) reported more swallowing problems after treatment, compared with their baseline scores. Using a complete case analysis, the change in MDADI score between baseline and 3 months was greater for CRT than for TLM ($p=0.029$, Mann–Whitney $U$ test), indicating a poorer patient-reported swallowing outcome for the CRT group. There was also evidence for a difference between the groups in the change in score for PSS Normalcy of Diet ($p<0.001$) and WST ($p=0.03$), but not for the MDADI ($p=0.20$).

### TABLE 2. Pretreatment and 3-month posttreatment swallowing scores for patients with both scores.

| Swallowing score | TLM mean (SD) [no. of patients] | CRT mean (SD) [no. of patients] |
|------------------|---------------------------------|---------------------------------|
|                  | median, interquartile range      | median, interquartile range      |
| Pre-MDADI        | 89.7 (11.7) [n = 21]             | 81.4 (17.2) [n = 26]             |
|                  | (93.7, 76.8–100)                 | (76.8, 64.7–99.7)                |
| 3-mo MDADI       | 77.9 (14.4) [n = 21]             | 59.1 (17.1) [n = 26]             |
|                  | (77.9, 69.5–88.4)                | (57.9, 47.4–73.7)                |
| Pre-PSS          | 93.5 (16.6) [n = 20]             | 88.9 (21.8) [n = 28]             |
|                  | (100, 100–100)                   | (100, 55–100)                    |
| 3-mo PSS         | 85.0 (21.9) [n = 20]             | 41.8 (32.8) [n = 28]             |
|                  | (90, 85–100)                     | (40, 10–50)                      |
| Pre-WST          | 18.5 (8.2) [n = 21]              | 16.8 (7.5) [n = 28]              |
|                  | (16.6, 10.8–25.0)                | (14.3, 11.1–22.5)                |
| 3-mo WST         | 17.9 (7.1) [n = 21]              | 11.4 (9.0) [n = 28]              |
|                  | (18.6, 12.2–25.0)                | (11.1, 2.0–19.2)                 |

Abbreviations: TLM, transoral laser microsurgery; CRT, chemoradiotherapy; MDADI, MD Anderson Dysphagia Inventory; PSS, Performance Status Scale Normalcy of Diet; WST, Water Swallow Test.

The multivariate repeated measures analysis based on all of the patients (assuming a normal distribution for the scores and using multiple imputation for the missing scores) found evidence for a difference between TLM and CRT in the change in score for the PSS Normalcy of Diet ($p<0.001$) and WST ($p=0.03$), but not for the MDADI ($p=0.20$).
Five patients in the CRT group were unable to complete the WST because of high risk of gross aspiration at 3 months and scored zero. No patients in the TLM group and none in either group at baseline scored zero.

**DISCUSSION**

This is the first study to assess swallowing function after primary TLM for oropharyngeal SCC using 3 different swallowing measures and to compare these with a matched group of CRT patients. It follows the methodology used by Patterson et al in analyzing the swallowing outcomes with CRT for all head and neck cancer sites; the oropharyngeal SCC cohort from this has formed the stage-matched comparison group for this study. The results of our preliminary, nonrandomized study suggest that patients treated by TLM had significantly better swallowing self-reported outcomes, diet texture scores, and swallow performance outcomes at 3 months after treatment than the matched CRT group. The differences in the results presented here may be attributable to decreased diffuse postradiotherapy scarring. Fibrosis of the musculature reduces the efficiency, coordination, and safety of the swallowing mechanism. It is a long-term condition, which can spread to surrounding tissues, thus progressively reducing function. Although the current study reports early postradiotherapy outcomes, patients seem to be functioning at a relatively high level and maintaining muscular condition, which may reduce the likelihood of chronic dysphagia.

When assessing swallowing function, it is important to realize that there is no single method of measuring outcomes. Patients’ experiences do not always correlate with objective measures. Therefore, both patient-reported and clinician-rated assessments were collected. These measures are routinely collected in our center. The current study did not include any swallowing instrumentation, as this was rarely indicated from clinical assessment. No one in the TLM group was unable to complete the WST, whereas in the CRT group, 5 patients could not complete the WST because of overt aspiration.

These data make a valuable contribution to the evidence based on swallowing function after oropharyngeal SCC. Comparing surgical and nonsurgical therapy in the setting of a controlled trial is challenging. It was encouraging to read that the concept of a phase III randomized controlled trial (RCT) comparing TORS with conventional CRT for oropharyngeal SCC was discussed at a United States national cancer meeting in 2011. Given that survival outcomes seem approximately similar, functional outcome is likely to be a primary outcome for such a trial. We believe that the combination of the MDADI, PSS Normalcy of Diet, and WST offer a straightforward and reproducible method of capturing patient-reported function and objective assessment in the clinical setting.

This study has deficiencies and the 2 groups may not be directly comparable. However, the results offer useful preliminary data for any RCT proposal. There seems to be a benefit in swallowing as measured by the PSS and WST with TLM and adjuvant therapy over historical CRT. The benefits, as measured by the MDADI, are less clear but there does seem to be a modest benefit with TLM. Not all patients in each group completed all 3 swallowing measures at the 2 time points. If a patient missed a test either pretreatment or at follow-up, this could not subsequently be rectified. Using multiple imputation to allow for missing data gave broadly similar results, but relied on an assumption of normality in the scores that is questionable.

The baseline difference between the 2 groups was significant for the MDADI, when all patients including those with missing data were analyzed. The statistical methods used to analyze the results take into account baseline differences, but, as mentioned earlier, the MDADI is unlikely to be a uniform scoring system. A difference of 10, although deemed a clinically significant difference, may not be equivalent from a start point of 89 compared to 81. Why this baseline difference exists in this current study is interesting. Options include: (1) Small sample sizes and chance. The baseline MDADI scores for TORS and CRT in the recent study by More et al. are equivalent and are more in line with the historic CRT cohort from this study. (2) Between 2006 and 2008, when the CRT patients were treated, TLM was not routinely offered in this center. This may have led to more extensive diagnostic biopsies. Now, a biopsy that does not breach the tumor margins is recommended with TLM in mind. As baseline swallowing measurements were usually taken about 2 weeks after biopsy, there may have been the potential for the biopsy sites to be more painful in the CRT group, thus lowering swallowing scores. (3) There has been a rapid rise in HPV-positive disease. It is possible that a greater proportion of TLM patients were HPV-positive than the CRT group. HPV-positive tumors are perhaps more discrete tumors, homogenous, and unlikely to be present in surrounding epithelial field change, which may mean they cause less swallowing impairment. (4) There was a higher proportion of advanced...
T classification disease (T3) included in the historical CRT group (13 of 33) compared to the TLM group (5 of 23). This could have led to a worse swallowing performance in the CRT group at baseline. However, our results do not support this suggestion for the MDADI or PSS.

(5) We must acknowledge the lack of N2 nodal subclassification in the CRT group. No patients with N2c disease were treated in the TLM group. It is difficult to conclude what effect the inclusion of patients with N2c disease in the CRT cohort would have had on the mean swallowing scores, other than to assume it would have worsened function. Clearly, N2c disease would have been treated with full dose RT to both sides of the neck.

We do acknowledge a lack of comparative basic data between the 2 groups (eg, smoking status, alcohol consumption, and comorbidities). We also recognize that a follow-up period of 3 months may be considered short. However, as mentioned earlier, swallowing at 3 months is a strong indicator of future performance. This study was intended to offer preliminary data. No clinically significant difference was established with a view to performing a sample size calculation in advance. However, for the purposes of an RCT, we would consider a difference of 10 on the MDADI to be a clinically significant difference.

Irrespective of whether the 2 groups are directly comparable, it seems apparent that patients treated pragmatically with TLM ± adjuvant therapy function well with respect to swallowing at 3 months posttreatment. If a score of 80 or more on the MDADI is considered to represent minimal or no swallowing problems, then a mean score of 78 at 3 months for a group of stage III and IVA oropharyngeal SCCs should be viewed positively. Likewise, the lack of any reduction in the objective WST in this group is impressive. We accept that 2 of 23 patients were treated with surgery alone and that only 4 had adjuvant CRT, but this is a pragmatic study and does represent the potential advantages of surgically staging the disease. This study is too small to make any meaningful conclusions on how surgery alone compares to TLM + RT and how this compares to TLM + CRT. These are questions that need addressing in the setting of an RCT and we hope that these data add to the planning of any such trial.

Attempting to form a conclusion on swallowing outcomes after oropharyngeal SCC treatment from the current evidence is challenging. Studies examining swallowing outcomes tend to be single institution series, small in number, lacking in homogenous data collection time points, and using a variety of swallowing measures have been used. One of the clear criticisms of this study is that we have compared TLM versus conventional RT techniques and not IMRT. More et al recently looked at the MDADI scores for 20 patients undergoing TORS + adjuvant therapy and 20 patients undergoing IMRT CRT for stage III and IVA oropharyngeal SCC. Both groups had a baseline MDADI score of 78, in line with this study’s CRT group. Swallowing was assessed at 3, 6, and 12 months, but for the TORS group, the 3-month score coincided with adjuvant therapy, whereas in our study, we looked at 3 months after completion of all therapy. Our study’s 3-month TLM results should therefore be viewed to be as equivalent time points to the 6-month scores in the study by More et al. Although the TORS group improved from an MDADI score of 62 at 3 months to 76 and 78 at 6 and 12 months, respectively, the CRT group MDADI scores were 56 and 57 at 3 and 6 months, rising to 60 at 12 months. The MDADI scores at 6 and 12 months statistically favored the TORS group. It is therefore evident that the conventional RT techniques used in our study led to very similar results to those of IMRT (59 and 56, respectively). However, at a recent meeting, Roe et al did present slightly more encouraging results with IMRT techniques for primary CRT for oropharyngeal SCC, among 62 patients of all stages and all head and neck sites (but as with most series, predominantly stage III and IV oropharyngeal SCC), the MDADI score rose to approximately 70 at 12 months posttreatment.

CONCLUSIONS

This study should be regarded as providing preliminary data. It suggests a benefit in swallowing self-reported outcomes, diet texture scores, and swallowing performance outcomes at 3 months after treatment with TLM ± adjuvant therapy compared to the nonrandomized historical CRT group. This adds to emerging evidence that primary TORS offers a benefit in swallowing function over primary CRT. However, only a sufficiently powered RCT will truly answer this question. This study may help provide the template for swallowing assessment and data to aid in planning of such a trial.

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