ORIGINAL ARTICLE

Outcomes Following Transoral Resection of Oropharyngeal Squamous Cell Carcinoma

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KEYWORDS
Oropharyngeal carcinoma; CO2 laser; Transoral surgery; Tonsil; Base of the tongue; Minimally invasive surgical techniques

Abstract
Introduction and objectives: The aim of our study was to evaluate outcomes of a minimally invasive approach, using transoral surgery (TOS) as the primary treatment for oropharyngeal carcinoma.

Methods: We reviewed 43 previously untreated patients with oropharyngeal carcinoma, who were treated with TOS. Distribution of the primary tumor site was: tonsil (52%), soft palate (23%), base of the tongue (21%) and posterior wall (4%). Eight patients had a stage I disease, 9 had a stage II disease, 7 had a stage III disease, 16 had a stage IVa, and 3 had stage IVb disease. Eighteen patients underwent postoperative radiotherapy. Records of these patients were reviewed to obtain measures such as local and regional control, overall and disease-specific survival, and speech and swallowing function.

Results: The overall recurrence rate was 44%, and the local recurrence rate was 18%. The 5-year overall survival and disease-specific survival rates were 55% and 66%, respectively. Five-year disease-specific survival rates by site were as follows: 100%, 85%, 44%, and 30% for posterior wall, tonsil, soft palate and base of the tongue, respectively. Five-year estimates for local control were 100%, 90%, and 0% for palate, tonsil and for base of the tongue tumors, respectively. All of the patients preserved the larynx and life without tracheotomy and oral alimentation was successful without feeding tube.

Conclusion: TOS as the primary treatment approach offers a surgical alternative for treatment of the primary oropharyngeal tumor, in the era of chemoradiation therapy. This approach confers a good local control and functional outcomes.

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Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) represents 15% of all head and neck cancers.1-3 The gold standard of treatment of these lesions remains unclear, with many treatment options, both surgical and nonsurgical approaches, supported by published experiences with no randomized trials.4,5 In early stages (stages I and II), the oncological results are similar after surgery or radiotherapy (RT) with anatomic and functional preservation.1,4 Two accepted oncological treatments have been currently established in advanced stages: surgical resection with or without postoperative (chemo) RT, and nonsurgical or organ preserving therapies, which utilize combinations of chemotherapy and RT. However, long-term follow-up studies have failed to demonstrate superior survival rates for each strategy. Furthermore, (chemo) RT is associated with a high rate of severe acute toxicities in the majority of patients,6 late swallowing dysfunction,7,8 and a mortality rate.8

Surgical strategies for patients with OPSCC continue to evolve. In the past, conventional surgical intervention for advanced OPSCC has been open surgery to the pharynx. With this approach, survivorship has been modest.9 Minimally invasive surgical techniques including transoral robotic surgery (TORS) and transoral surgery (TOS) are less invasive and offer impressive functional and oncologic outcomes.10,11 As experience with TOS increases, its value in managing OPSCC is becoming more apparent.12 However, detractors of TORS suggest that this technique is not currently available in all centers and the cost and availability of other minimally invasive approaches may obviate the need for robot-assisted approaches.13

To clarify the effectiveness of TOS as a primary surgery modality, in this study, we examine our result with the use of TOS with or without neck dissection and with or without adjuvant (chemo) RT in the treatment of OPSCC, and we describe the functional and oncological results of the procedure, comparing our results with other reports.

Methods

Between January 1999 and November 2009, 43 previously untreated patients with OPSCC (including the tonsil, tongue base, soft palate and pharyngeal wall) underwent surgery at our Department. Exclusion criteria included prior diagnostic tonsillectomy, tumors resected with an associated transcervical approach, as well as patients who developed recurrence after RT. Written informed consent was obtained from each patient.

All patients who underwent a surgical procedure were carefully evaluated before operation. In all cases the treatment choices were discussed at the regular institutional head and neck multidisciplinary meeting. The decision to proceed with a surgical rather than a nonsurgical treatment option was a joint one between both patient and clinician.
In TOS no strict exclusion criteria apply; however, relative contraindications include patient or tumor factors that might result in inadequate endoscopic access or tumor exposure. All patients had complete exposure of the lesion and underwent TOS with curative intent either with monopolar diathermy resection or CO₂ laser. Patients with lateral lesions (52%) underwent a transoral lateral oropharyngectomy, according to the technique described by Holsinger et al., and the remaining patients had a conventional transoral resection. In either case, the resection was performed under direct vision and palpation, with the exception of base of the tongue tumors, where an operating microscope was used.

The medical records of these 43 patients were retrospectively reviewed. Swallowing function before and after TOS was measured with a clinically relevant functional outcome swallow scale. The stage of the disease was determined after the surgical resection of the tumor according to the TNM system of the International Union Against Cancer (7th edition). The histologic grade was determined according to the degree of differentiation of the tumor (Broders’ classification). The clinicopathologic data from the patients are shown in Tables 1 and 2.

Indications for neck dissection in TOS are unchanged compared with those of other primary surgical techniques. The indications for performing a selective neck dissection were absence of identifiable metastatic neck nodes or intraoperative finding of positive nodes without extracapsular spread. Generally, ipsilateral neck dissections were carried out in patients with unilateral tumors with or without palpable neck nodes, or without involvement of the midline and no clinical disease in both sides of the neck. All the remaining patients received a bilateral neck dissection. Neck dissection was performed on 37 patients (86%) (Table 3). A total of 18 (42%) patients received postoperative RT. As a general rule, indications for adjuvant RT were nodal extracapsular extension, bulky or multiple positive nodes (N2 or greater), positive or close (<5 mm) tumor margins, lymphovascular invasion seen at the primary site or locally advanced stages (T4).

Human papillomavirus (HPV) detection analysis was performed in all samples with OPSCC as described in detail previously. HPV genomic sequences were detected by polymerase chain reaction (PCR) amplification by use of consensus degenerate primers MY09/MY1119 and GP5+/6+ complementary to the conserved L1 region. All tumor DNAs were also tested for HPV16 and HPV18 by amplification of the viral E6 and E7 region by use of type-specific primers (HPVONC 1/HPVONC 2). Positive control samples and negative control samples were applied in all analyses. The products were analyzed by electrophoresis on 2% agarose gels, stained with ethidium bromide.

End points analyzed were local control, locoregional control, disease-specific survival (DSS) and overall survival (DFS). The statistical analysis was performed with SPSS statistical software (version 19.0 for Windows; SPSS, Chicago, IL). Statistical analysis was performed using chi-square and Fisher’s exact tests. Survival curves were calculated using the Kaplan–Meier product limit estimate. Differences between survival times were analyzed by the log-rank method. Multivariate Cox proportional hazards models were
used to examine the relative impact on outcome of the variables demonstrated to be statistically significant in univariate analysis. A \( p \) value \( \leq 0.05 \) was considered to be statistically significant. All patients involved in this study were followed for a minimum of 2 years.

**Results**

The median follow-up of the whole series was 67 months (range, 8–162 months), and the median follow-up of the patients alive until their last visit was 112 months (range, 36–162 months). No patient died in the immediate postoperative period due to complications related to surgery. No HPV DNA was seen in any of the 43 samples of OPSCC studied.

Recurrent disease developed in 19 patients (44%): 3 patients (7%) developed local recurrence alone, 4 patients (9%) neck recurrence alone, 3 (7%) local and regional recurrences, 2 (5%) loco-regional recurrence and distant metastasis, and 7 (16%) distant metastasis alone. The median time for developing a recurrence was 14 months. In addition, 4 patients (9%) developed a second primary tumor. The 5-year locoregional control rate was 41%. The incidence of local recurrences was more frequent in \( pT2 \) and occurred in the only \( pT4 \) tumor (\( p = 0.069 \); Table 4). Recurrences were more frequent in those tumors located in the base of the tongue (77% of tumors) (\( p = 0.026 \); Table 5). Neck recurrence was more frequent in \( pN1 \), although the differences did not reach statistical significance (\( p = 0.575 \); Table 6). The administration of postoperative RT resulted in better 5-year loco-regional control: 60% in irradiated patients vs 24% in non-irradiated patients (\( p = 0.116 \)). Recurrence rates were also higher in less differentiated tumors, although differences were not significant (\( p = 0.468 \)) (Table 7).

Of the 20 patients who received unilateral neck dissection, 5 (25%) (2 primary tumors of the base of tongue, 2 of the tonsil and 1 of the soft palate) had regional recurrence (4 ipsilateral and 1 contralateral), whereas 3 of the 17 patients (18%) (2 primary tumors of the soft palate and 1 of the base of tongue) who received bilateral neck dissection had regional recurrence (\( p = 0.860 \)). Only one (with a primary tumor of the base of tongue) of the 6 patients (17%) who did not receive any neck dissection experienced regional recurrence. The regional recurrence rate varied significantly depending on the use of adjuvant RT: 66% of regional recurrences had not received postoperative RT (\( p = 0.042 \)). Extracapsular spread was present in 13 patients (30%) who received a neck dissection; those patients had higher incidence of neck recurrence (31% vs 17%; \( p = 0.04 \)) than the patients without extracapsular spread. Distant metastases were significantly associated with nodal spread and they were present in 10% of the \( pN0–1 \) patients and in 47% of the \( pN2–N3 \) (\( p = 0.035 \)).

Histopathologic examination showed microscopic involvement of the surgical margins in 9 patients (21%).

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**Table 3** Neck Dissection in Function of the Primary Tumor Site.

<table>
<thead>
<tr>
<th>Primary Tumor Site (n)</th>
<th>No. (%)</th>
<th>Selective (%)</th>
<th>Radical (%)</th>
<th>Selective and Radical (%)</th>
<th>Selective Bilateral (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral pharyngeal wall and tonsil (22)</td>
<td>1 (5)</td>
<td>13 (59)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall (2)</td>
<td>1 (50)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Tongue base (9)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>3 (33)</td>
<td>2 (22)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Soft palate (10)</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>1 (10)</td>
<td>5 (50)</td>
</tr>
</tbody>
</table>

**Table 4** Local Recurrence in Function of the pT Classification.

<table>
<thead>
<tr>
<th>pT Classification (n)</th>
<th>No. of Patients With Local Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (14)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>T2 (18)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>T3 (10)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>T4 (1)</td>
<td>1 (100)</td>
</tr>
</tbody>
</table>

**Table 5** Recurrence in Function of the Primary Tumor Site.

<table>
<thead>
<tr>
<th>Primary Tumor Site (n)</th>
<th>Local (%)</th>
<th>Regional (%)</th>
<th>Loco-regional (%)</th>
<th>Loco-regional and Distant (%)</th>
<th>Distant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral pharyngeal wall and tonsil (22)</td>
<td>1 (5)</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Posterior pharyngeal wall (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tongue base (9)</td>
<td>2 (22)</td>
<td>0 (0)</td>
<td>2 (22)</td>
<td>2 (22)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Soft palate (10)</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>3 (30)</td>
</tr>
</tbody>
</table>
patients (23%) in the positive margin group and 6 patients (17%) in the negative margin group had local recurrence (p=0.541).

Local and/or regional recurrences were surgically treated in 3 patients, and only 1 remains free of disease. In 2 patients, the recurrence was treated with surgery and RT, and both were successfully salvaged. Two patients received RT alone and 4 patients received chemo-RT and all of them have died. The remaining 7 patients received palliative treatment (patients with distant metastasis or patients previously irradiated with unresectable disease).

At the end of the follow-up period, 19 patients (44%) were alive without evidence of disease, 16 patients (37%) died due to the disease, and 8 patients (19%) died due to unrelated causes. The 5-year overall survival (OS) and disease-specific survival (DSS) rates for all 43 patients were 55% and 66%, respectively. Five-year DSS rates by stage were as follows: 100%, 82%, 57%, 44%, and 50% for stages I to IVA and IVB, respectively (p=0.045; Fig. 1). Five-year DSS was 100%, 85%, 44% and 30% for posterior pharyngeal wall, tonsil, palate and base of tongue, respectively (Fig. 2). The 5-year local disease-free survival (DFS) by primary site was 100% for soft palate tumors, 90% for tonsil tumors and 0% for base of tongue tumors (Fig. 3).

Multivariate Cox proportional hazards model included pT classification, pN classification, degree of differentiation, localization and extracapsular spread. These models showed only one parameter that was statistically significant independent predictor of a reduced DSS: presence of extracapsular spread (hazard ratio [HR]=1.879; 95% confidence interval [CI], 1.902–3.911; p=.001).
RT regimens on survival and functional preservation has never been tested against the surgical approaches in a randomized controlled trial.\textsuperscript{20,21} Critics of surgical treatment point to the effectiveness of primary (chemo) RT and question the role of primary surgery because many patients will receive adjuvant RT anyway. Furthermore, although chemoradiation was once thought to be a way of preserving organs, this outcome has now been shown to fall off markedly in addition to low survival rates in patients, 5 years from treatment.\textsuperscript{22} To compound this problem, it has been confirmed by mature cooperative group analyses that (chemo) RT treatment protocols carry high rates of acute and late, prolonged "toxicities", or side effects of treatment, the most common of which is swallowing dysfunction, which carries its own mortality independent of disease.\textsuperscript{23}

Minimally invasive surgery seems to confer excellent oncologic prognosis with reduced treatment-related functional loss and cost for patients. Moreover, surgery, as primary therapy, includes complete pathologic staging for determination of patient prognosis, as well as the potential for sparing some patients subsequent (chemo) RT with its attendant toxicity. Currently, TOS is challenging the dogma that lower morbidity is associated with nonsurgical treatment. TOS to the oropharynx has traditionally been limited to those tumors that can be directly visualized and manipulated with standard instrumentation and lighting. Because of line-of-sight limitations for tumors in the base of the tongue, transoral approaches were reserved for smaller lesions of the tonsil and palate. However, as experience with TOS increases, its value in managing OPSCC is becoming more apparent.

In contrast to nonsurgical protocols, patient eligibility for TOS is broad and is not necessarily constrained by medical factors. Limitations to TOS include inadequate endoscopic access (which is rare for the oropharynx) or projected unresectability, because of a probable positive margin, like lateral extension of tonsil tumors through the infratemporal fossa to invade the great vessels or ventral extension of tongue base tumors into the anterior floor of mouth. So, it is not the advanced T or N classification of disease but the patient’s anatomy and/or tumor extent that may limit the use of TOS as a primary treatment.

Smaller TOS studies encompassing the full range of, but with predominantly earlier T classifications and limited follow-up, have been published.\textsuperscript{24} Most OPSCC, however, present at an advanced overall stage, as in our series. Recently some studies have shown successful results for advanced-stage OPSCC treated with TOS +/- adjuvant therapy.\textsuperscript{11,25} Although studies may differ from ours in proportions of T classification or reporting of positivity for HPV biomarkers, those that are comparable reveal very similar oncologic outcomes. Limited-stage OPSCC carcinomas (T1–T2, N0–1) can be treated with surgery or RT with similar survival and functional outcomes.\textsuperscript{14,26} The local recurrence estimate after RT varied from 13% to 32% in patients classified as T1–T2.\textsuperscript{26} These figures are similar to our experience using TOS (19%).

Haughey et al.\textsuperscript{11} performed a multicenter study in US with a series of 204 patients with advanced OPSCC. They provide a strong evidence for the efficacy of TOS as primary

The mean hospital stay was 4 days (range, 2–23 days). Fifteen patients (34%) had a complication after surgery. The most common complication was minor postsurgical hemorrhage, which occurred in 10 cases (23%). The bleeding settled without further intervention. Surgical wound infection was present in 2 patients (5%). Pneumonias were present in 2 patients (5%). No patient died as a result of these complications. A tracheostomy was performed during surgical procedures in 2 patients (5%) and both could be sealed. So, no patients required a permanent tracheostomy. The oral feeding was successfully recovered in all patients. Of the 43 patients, 33 had normal or near-normal (stage 0 or 1) swallow function and 10 patients had stage 2 swallow function (stable with a modified diet only). The mean duration of enteral nutritional support via feeding tube was 7 days (range, 4–23 days).

Discussion

OPSCCs are usually diagnosed at advanced stages.\textsuperscript{18} This is also reflected in our series, in which 60% of the patients were in stages III–IV. The challenge in this scenario is to choose the correct modality of treatment for each patient, and in many cases there is an absence of Level I evidence to guide treatment decisions.

The oncogenic HPV, especially HPV16, has been associated with this type of cancer and appears to be linked to better clinical outcomes than in smoking patients, regarding patient survival. Nevertheless, according to the low proportion of HPV-related OPSCC in our environment,\textsuperscript{19} HPV does not seem to play a major role in the cancer development among the patients included, although this cannot be known for certain.

Nonsurgical approaches to management of OPSCC grew in popularity because it seems to avoid the postoperative morbidity of traditional open approaches to the oropharynx. However, in OPSCC the impact of current (chemo)
treatment approach for advanced OPSCC. They demonstrated 2- and 5-year OS estimates of 89% and 78%, DSS estimates of 91% and 84%, and DFS estimates of 85% and 74%, respectively. And their local control rate was greater than 90%, although most of the patients received adjuvant RT. In addition, in the study of Grant et al.,10 the patients in advanced stages who did not receive postoperative RT also have excellent locoregional control and DFS (86%) rates. In the present series TOS controlled the disease at the primary site in 35 of 43 patients and our overall local control rate was 82%, either in early-stage as in advanced-stage tumors. Huang et al.27 reported a series of 71 patients who underwent (chemo) RT (32% T3 and T4 cases), with a locoregional control rate of 90% (salvage surgery included), but a gastrostomy tube rate of 35%. In the current study with 25% T3 and T4 tumors, locoregional control was 82%, and no patient was long term feeding tube dependent.

The results in terms of local control seem to be influenced by the primary site. Our estimated 5-year local control rate was 90% for tonsil tumors, in contrast with a 33% local control rate for base of the tongue cancers. It is known that treatment of malignant carcinomas of the base of the tongue is characterized by poor prognosis. However some authors reported excellent local and regional control and minimized morbidity using TOS, with 5-year local control rates up to 85% without local recurrences in T1-T2 tumors and a 20% of local recurrence rate in T3-T.28 Our poor results in this small group of patients do not invalidate the use of TOS and indicate that base of tongue tumors represents a higher risk and should be resected by surgical teams with significant experience. In contrast, our series proves that TOS provides an effective treatment for SCC of the tonsillar region, soft palate and posterior wall of the pharynx with 5-year local control rates higher than 85%.

Extracapsular spread from metastatic nodes achieves prognostic significance in either the univariate or multivariate analysis for DSS. This finding has been reported in other OPSCC series.11 Patients with extracapsular spread are considered at high risk and may qualify for adjuvant treatment with (chemo) RT. The negative impact of higher T classification on prognosis is expected and is frequently seen in other studies. The fact that we had a lower T3 and T4 prevalence than is often seen in some nonsurgical studies of advanced OPSCC disease may be attributable to staging "creep" created by clinical staging vs the pathologic staging available from surgical specimens. This concept is especially pertinent when staging base of tongue tumors by imaging/scanning, since lingual tonsillar tissue may be difficult to distinguish on CT or MRI from tumor, and may be erroneously included in tumor measurements.11 As it is observed in other studies we observed the negative impact of high N classification on the development of distant metastasis and on prognosis. Some authors recommended carrying out bilateral lymph node dissections in OPSCC. However, in selected cases (T1–T2 N0 with no invasion of the midline), it is possible to perform an ipsilateral lymph node dissection without compromising regional control. As in other works,29 we found that the factor that best predicts the development of distant metastases is the pN classification, since these were present in 47% of patients classified as pN2–N3.

Positive margins are usually associated with higher local recurrence rate, which motivates the TOS surgeon to pursue a microscopically negative margin if at all possible, even to the extent of returning patients to surgery for re-resection. However, we did not observe a relationship between microscopic involvement of the surgical margins and local recurrence. This may be attributed to the effect of postoperative RT, which was administered to all the patients with surgical margin involvement.

We had good results in our series in terms of local control, mainly in tumors that did not involve the base of the tongue, and the rate of local recurrence was low and compare favorably with the benchmarks. However our results are poorer than those reported in other surgical series in terms of locoregional control due to the high rate of regional recurrence. The 3-year locoregional control for TOS in advanced OPSCC varies from 80% to 96%.30 In the current study, the 5-year local DFS rates (100% for palate, 90% for tonsil and 0% for base of the tongue tumors) could suggest that TOS provides a good local control for patients with tumors of the tonsillar region and soft palate. Only selected tumors of the base of the tongue would be amenable for this technique. In the largest published series for TOS approach to OPSCC available to date,31 the 3-year OS, DSS, and DFS were, respectively, 86%, 88%, and 82%. These figures are better than those observed in our series (67%, 77% and 32%, respectively). The 5-year DSS rates (43%) confirm that advanced OPSCC has aggressive behavior with poor prognosis. The low rate observed in our study may be due to the high proportion of patients who developed a regional recurrence, distant metastasis and second primary tumors. These differences could be attributable to differences in adjuvant chemotherapy and differences in the population of the reported series. In this manner, our series includes a higher proportion of patients with adverse pathologic factors (large tumors, advanced nodal disease, extracapsular invasion, etc.). On the other hand, our oncological results are similar to those reported with other treatment modalities like (chemo) RT. The results of the randomized trial of the Groupe d’Oncologie Radiotherapie Tete et Cou (GORTEC 94-01)31 comparing RT with concomitant chemoRT in patients with locally advanced (stages III and IV) OPSCC showed a 5-year DFS and local-regional control rates associated with concurrent chemoRT and RT alone of 27% and 15% and 48% and 25%, respectively. The 5-year DFS of our patients was 21% and local-regional control rate was 41%.

Despite 42% of patients receiving adjuvant RT, adequate oral intake was maintained in all subjects. This result contrast with the long-term swallowing dysfunction rate (43%) reported from chemoradiation studies.32 No patient needed long term tracheotomy. The optimal functional recovery and swallowing outcomes observed in our study reinforces the fact that TOS is an important step in the functional organ preservation in the management of OPSCC.

**Conclusion**

Our results confirm, based on valid comparisons, that TOS, as the primary treatment approach, offers a surgical alternative for treatment of the primary tumor, and potentially
avoids the acute and chronic threat to upper aerodigestive tract function posed by high-dose RT targeted at the pharynx, often sensitized to an even greater functional impact by concurrent chemotherapy. Oncological results are modest but similar to other therapeutic modalities such as radiation and chemoradiation, and we believe that it can be recommended within the therapeutic modalities of choice for the treatment of such patients.

Conflicts of Interest

The authors have no conflicts of interest.

References

