The Laryngoscope

Transoral Laser Microsurgery (TLM) ± Adjuvant Therapy for Advanced Stage Oropharyngeal Cancer: Outcomes and Prognostic Factors

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Objectives/Hypothesis: Document survival, prognostic variables, and functional outcomes of patients with AJCC stage III or IV oropharyngeal cancer, treated with transoral laser microsurgery (TLM) ± adjuvant therapy.

Study Design: Analysis of prospectively assembled data pertaining to the above-described patient cohort.

Methods: Patients treated with TLM for AJCC stage III or IV oropharyngeal cancer at Washington University School of Medicine from 1996 to 2006 were followed for a minimum of 2 years. Recurrence, survival, functional, and human papilloma virus data were analyzed.

Results: Eighty-four patients met inclusion criteria. Mean follow-up was 52.6 months. Overall AJCC stages were: III 15% and IV 85%. T stages were T1–2, 74%; T3–4, 26%. Eighty-three patients underwent neck dissection, 50 received adjuvant radiotherapy, and 28 received adjuvant chemoradiotherapy. Overall survival at 2 and 5 years was 94% and 88%, respectively. Disease-specific survival at 2 and 5 years was 96% and 92%, respectively. Six patients recurred (7%): locally (one), regionally (four), and distant (five). T stage, positive margins, and p16 status significantly impacted survival. The addition of adjuvant chemotherapy in high-risk patients did not significantly impact survival. Five patients (6%) had major surgical complications, but without mortality. Eighty-one percent of patients had acceptable swallowing function at last follow-up. Immediately postoperatively, 17% required G-tubes, which dropped to 3.4% of living patients at 3 years.

Conclusions: In this population, our findings validate TLM ± adjuvant therapy as a highly effective strategy for survival, locoregional control, and swallowing recovery in AJCC stage III and IV oropharyngeal cancer. Our finding also show that p16 positivity improves survival.

Key Words: Transoral laser microsurgery, tonsil, tongue base, advanced stage oropharyngeal cancer, chemoradiotherapy, human papilloma virus, p16.

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INTRODUCTION

It was estimated that over 35,000 people were diagnosed with oral cavity and oropharyngeal cancer in the United States in 2008.[1] Over the past decade there has been an increase in the incidence of oropharyngeal cancer, especially among individuals under the age of 45 years,[2] which has been attributed to human papilloma virus (HPV) infection.[3] Nonsurgical or organ preserving therapies, which utilize combinations of chemotherapy and radiotherapy (RT), have become popular treatments for advanced stage oropharyngeal cancers. However, long-term follow-up studies have failed to demonstrate superior survival rates. In addition, RT with concurrent chemotherapy is associated with a high rate of severe acute toxicities in the majority of patients,[4] late swallowing dysfunction,[5,6] and a mortality rate.[4]

Transoral laser microsurgery (TLM) is a minimally invasive, but maximally resectional endoscopic surgical technique that offers a locally targeted treatment, relatively rapid recovery, and a low long-term toxicity

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profile.[7,8] Starting as a treatment for very limited head and neck malignancies,[9] its scope has now been broadened to include advanced T-stage disease at a variety of sites in the upper aerodigestive tract.[8,10] Thus far, the majority of published studies investigating the role of TLM in treating oropharyngeal cancer have been small, with limited follow-up, and none have specifically addressed American Joint Committee on Cancer (AJCC) stages III and IV oropharyngeal cancer, which is now one of the most common groups presenting to head and neck cancer treatment centers. Furthermore, we are not aware of a TLM study that has controlled for the potential impact of HPV biomarkers on outcomes in advanced stage disease.

We thus present a large, mature study of TLM with adjuvant therapy, which investigates long-term survival and functional outcomes plus an array of relevant prognostic variables.

MATERIALS AND METHODS

Study Design and Population

A prospective, computerized database (Excel software; Microsoft Corp, Redmond, WA) of head and neck cancer patients treated with TLM at Washington University Medical School of Medicine (WUSM) in St. Louis, Missouri has been maintained since June 1996. The Human Research Protection Office at WUSM approved the database as well as this specific research protocol, and patients were consented prior to enrollment into this database. Staging, treatments, outcomes, and complications as they occurred for each patient were recorded in the database. From this database, patients were searched and selected for the study we report here, who had undergone TLM by the senior author (B.H.H.) with curative intent for a biopsy-proven, AJCC stage III or IV oropharyngeal cancer (T3N0, T1–3N1, T4aN0–1, T1–4aN2, T4a, N3; hereafter referred to as advanced oropharyngeal cancer) from June 1996 through August 2006. Patients were included who had undergone diagnostic tonsillectomy, diagnostic excisional neck biopsy, or prior neck dissection by a department member, and were subsequently referred to the senior author for definitive TLM management. Patients were excluded who had a prior history of head and neck aerodigestive tract cancer or evidence of distant metastasis at presentation.

In contrast to nonsurgical protocols, eligibility criteria for TLM are broad and are not necessarily constrained by age, hematological, biochemical, or performance status criteria. Relative contradictions to TLM include inadequate endoscopic access, which is rare for the oropharynx. These can be thought of as the 8 Ts of endoscopic access: teeth, trismus, transverse dimensions (mandibular), tori (mandibular), tongue, tilt (atlanto-occipital extension), treatment (prior radiotherapy), and tumor. Another contraindication to TLM is projected unresectability due to potential for positive margin (e.g., skull base extension via the infratemporal fossa). During these time points there was no record of how many patients were not considered eligible for TLM, although our clinical impression remains that that number is in single digits. Patients who required microvascular free flap reconstruction were not excluded. The senior author has developed techniques for setting in and suturing free flaps through the mouth, with the pedicle exiting to the neck through a small pharyngotomy. Information from the prospectively gathered data was confirmed by careful review of electronic and paper medical records, national death registries, and direct telephone contact with patients to update and verify status. N stage was determined from pathologic results, and T stage was determined primarily by clinical staging, unless operative findings upstaged the disease (e.g., extension to the extrinsic tongue musculature or pterygoid muscles), in which case the pathologic staging was used.

Treatment

Primary tumor/TLM. All surgeries were performed by the senior author, following principles of TLM set forth by Steiner and Ambrosch.[8,10] The role of TLM in this patient cohort was to completely eliminate all known oropharyngeal and neck malignant disease, to a negative microscopic margin. In TLM, a modified laryngoscope, or gag style retraction device is inserted into the patient's mouth to expose the primary tumor. An operating microscope or rod telescope is utilized to illuminate and magnify the operative field, and to discern clearly between healthy versus tumor tissue in the depths of the resection bed. The tumor is excised with a CO_2 laser (either free beam or fiber delivered), which allows precision cutting with minimal charring and oozing. The tumor is deliberately transected at a series of locations in order to map deep extension along the invading front. A reasonable margin of normal tissue, usually at least 1 cm, is excised beyond the invading front of the tumor, and then the specimen is removed in two or more pieces as a multibloc resection. Peripheral excision margins of the resected tissue are determined by the surgeon and inked in the operating room to allow orientation and further analysis by pathologists.

Frozen sections from the resection defect are routinely used to verify complete removal, or to direct further laser resection of invisible residual microscopic disease. Regions where we detect this latter pattern are the styloid apparatus in large tonsil tumors that invade into the pterygoid space, and the anterior floor of mouth/submandibular gland structures in large base of tongue tumors. These extensions are seldom seen on any modality of image (although magnetic resonance imaging is best), creating a potential for "miss" when closely targeted RT planning is utilized in nonsurgical treatment approaches. TLM allows for controlled and complete primary tumor excision in most cases, with maximal preservation of normal tissue and function.

Neck dissection and adjuvant therapy. Neck dissections were performed based on the presence or absence of cervical lymphadenopathy or risk of occult metastasis. Levels 2 through 4 lymph nodes were removed in all dissections and extended to level 1B if the primary tumor invaded the floor of mouth from the tongue base. Retropharyngeal lymph nodes were removed during primary resection. Administration of adjuvant therapy was determined at a multidisciplinary tumor board, based upon pathology reports of extracapsular spread (ECS) from nodal metastasis, two or more positive or contralateral lymph nodes, positive margins, patient preference for chemotherapy, and an array of hematological, biochemical, and performance status criteria.

HPV Detection

The preferred determination of HPV status in head and neck cancers is a controversial issue. In our study, we used immunohistochemical staining for p16 and in situ hybridization (ISH) for HPV DNA. Secondary to action of the HPV-derived E7 oncogene effect on the retinoblastoma gene, p16 is overexpressed.[11,12] All tumors were analyzed by the study pathologist (J.S.L.) without knowledge of clinical status, follow-up, or outcome. Immunohistochemical staining for p16 was performed using p16 monoclonal antibody (MTM Laboratories CINTEC,

TABLE I.
Functional Outcome Swallowing Scale.[13]

Stage	Symptoms
0	Normal function and asymptomatic.
1	Normal function with episodic or daily symptoms of dysphagia.
2	Compensated abnormal function manifested by considerable dietary modifications or prolonged mealtime (without weight loss or aspiration).
3	Decompensated abnormal function with weight loss of 10% of body weight over 6 months owing to dysphagia or daily cough, gagging, or aspiration during meals.
4	Severely decompensated abnormal function with weight loss of 10% of body weight over 6 months owing to dysphagia or severe aspiration with bronchopulmonary complications. Nonoral feeding for most nutrition.
5	Nonoral feeding for all nutrition.

Westborough, MA) and either DAKO LSAB2 horseradish peroxidase system (DAKO Corp., Carpinteria, CA) or Ventana Autostainer (Ventana Medical System Inc., Tucson, AZ). All cases showed either no staining or >75% of tumor cells positive. In situ hybridization was performed using ISH I View Blue Plus Detection Kit (Ventana Medical System Inc.), which hybridizes with high-risk HPV genotypes 16, 18, 33, 35, 45, 51, 52 56, and 66. Any definitive nuclear staining in the tumor cells was considered positive. Cases were classified in a binary manner as either positive or negative for both p16 and ISH.

Statistical Analysis

Primary endpoints for this study were overall survival (OS) and disease-specific survival (DSS). Secondary endpoints were HPV status (p16, ISH), patterns of failure (local, regional, distant), ECS from neck nodes, and swallowing function as determined by gastrostomy tube (G-tube) placement and Functional Outcome Swallowing Scale (FOSS).[13] FOSS ranks swallowing function from 0 to 5, with 0 being normal function and 4–5 being G-tube-dependent (Table I). Stages 1 and 2 represent normal swallow function with episodic or daily symptoms of dysphagia, and are considered acceptable. Overall survival was defined as the time from surgery to the date of death due to any cause. Disease-specific survival was defined as the time from surgery to the date of death from oropharyngeal cancer. Disease-free survival (DFS) was defined as the time from surgery to the date of any recurrence of oropharyngeal cancer or death. Survival data were analyzed using Kaplan-Meier (KM) method and statistical significance determined by log-rank test. To adjust for covariate effects and calculate hazard ratios, Cox proportional models were developed when appropriate. In the multivariate analysis, Cox proportional model was used to adjust for variables of statistical significance from the univariate analyses. All statistical tests were 2-sided and a P value of .05 or less was considered significant. All analyses were performed using SAS 9.1.3 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Of the 253 patients registered in the TLM database from June 1996 to August of 2006, 104 patients were treated for oropharyngeal cancer. Of these patients, nine were AJCC stage I or II, and 11 patients had a history of prior head and neck cancer, all of whom were excluded. This left 84 patients for analysis in the study. Table II shows the characteristics of these patients. Mean and median follow-up were 52.6 months and 48.5 months, respectively (range, 2–132 months). Five patients had <24 months follow-up, all because of death within 2 years from entry into the study. Three patients died at 2, 10, and 18 months postoperatively from recurrences; one patient died of lung cancer at 12 months, and one patient died of non–head and neck cancer causes at 7 months. Primary sites involved were base of tongue, 46 patients; palatine tonsil, 37 patients; and soft palate, one patient. The one soft palate case was grouped with the tonsil patients. Eight patients (10%) underwent surgery at an outside facility prior to referral to WUSM for definitive TLM treatment (five had neck biopsies, one had tonsillectomy and neck mass excision,

TABLE II.
Patient Characteristics Stratified by Tumor p16 Status.

Characteristic	Total, n=84	p16 Positive,* n=69	p16 Negative,* n=4
Age, yr			
Mean (range)	56.0 (35–81)	56.4 (35–81)	56.3 (45–67)
Sex (%)			
Male	74 (88)	62 (90)	3 (75)
Female	10 (12)	7 (10)	1 (25)
Tumor subsite (%)			
Base of tongue	46 (55)	38 (55)	1 (25)
Tonsil and soft palate	38 (45)	31 (45)	3 (75)
AJCC stage (%)			
III	13 (15)	10 (14)	2 (50)
IV	71 (85)	59 (86)	2 (50)
T stage (%)			
T1	29 (35)	24 (35)	0 (0)
T2	33 (39)	25 (36)	3 (75)
T3	15 (18)	13 (19)	1 (25)
T4	7 (8)	7 (10)	0 (0)
N stage (%)			
N0	3 (4)	3 (4)	0 (0)
N1	12 (14)	9 (13)	2 (50)
N2	64 (76)	54 (78)	1 (25)
N3	5 (6)	3 (4)	1 (25)
Smoking status (%)			
Never	32 (38)	28 (41)	0 (0)
Ever	50 (60)	39 (57)	4 (100)
Unknown	2 (2)	2 (3)	0 (0)
Alcohol consumption, oz/wk (%)			
0–32	36 (43)	29 (42)	1 (25)
>32	47 (56)	39 (57)	3 (75)
Unknown	1 (1)	1 (1)	0 (0)

*p16 data available on 73 patients.
AJCC = American Joint Commission on Cancer; T stage = tumor stage; N stage = nodal stage.

one had tonsillectomy, and one had a neck mass, thought benign, removed 2 years prior).

Of the 84 patients in the study, p16 staining data were available for 73 patients (87%), with 69 (95%) staining positive for p16 and four (5%) negative. HPV ISH staining were available for 78 patients (93%), with 60 patients staining positive (77%) and 18 negative (23%). Patient characteristics stratified by p16 status are shown in Table II.

Extracapsular spread data were available for 79 patients (94%). Of these patients, 67 (85%) had ECS. Eighty-four percent of p16 positive cancers and 75% of HPV ISH positive cancers had positive ECS.

Treatment

All surgical resections were completed, i.e., none were abandoned for salvage radiotherapy and/or chemotherapy. Seven (8%) of 84 patients were completed as open procedures through a small pharyngotomy created at the time of the simultaneous neck dissection, to remove minimal gross or microscopic tumor residue not accessible transorally. Ten patients (12%) had microscopic positive margins reported on permanent pathological analysis following the initial resection. Of those patients, five had negative margins following re-resection, one patient had positive margins despite three additional resections, and data were not available for one patient. The mean hospital stay was 4.3 days (range, 1–23).

Neck dissections were performed in 83 patients (99%), ipsilateral in 75 patients (90%), and bilateral in eight (10%). Seventy-eight patients (93%) received adjuvant therapy; 50 received adjuvant RT and 28 received adjuvant chemoradiotherapy. Because some patients received RT at outside facilities, the type of RT administered was not available for all patients. Of those receiving RT at Washington University, approximately 93% received intensity modulated radiation therapy (IMRT).

Complications

Primary tumor/TLM. There were no treatment-related deaths. Five patients (6%) had surgical complication requiring further surgery. Three patients experienced significant bleeding requiring return to the operating room, which occurred at postoperative days 3, 6, and 27, respectively. One patient had a pharyngeal wound breakdown. During reresection for positive margins, the airway was lost on one patient necessitating an operative cricothyrotomy. One patient developed bilateral hypoglossal nerve paresis, a documented stretch-related complication of endoscopic approaches to the pharynx (e.g., tonsillectomy).[14] Nine patients demonstrated postoperative velopharyngeal incompetence, although none severe enough to prevent oral intake or good speech intelligibility. A fasciocutaneous flap can be used if one half the full thickness of the soft palate is resected or if the resection includes the retromolar trigone, in which scarring often pulls the soft palate anteriorly away from the posterior pharyngeal wall. Tracheotomy was performed at the time of TLM or within 30 days of surgery in nine patients (11%), and after 30 days in one patient.

Neck dissection and medical complications. Of the 83 patients who underwent neck dissections, there were four spinal accessory nerve injuries, three neck infections, two chyle leaks, two seromas, two hematomas treated conservatively, one hematoma requiring return to the operating room, and one perioperative pulmonary embolism.

Adjuvant therapy. Five patients developed late radiation-induced esophageal stenosis, two trismus, two osteoradionecrosis of the mandible, and one late radiation necrosis of the pharynx and parapharyngeal space, necessitating free flap reconstruction.

Survival Outcomes

The 2-year and 5-year estimates of OS were 94% (95% confidence interval [CI], 86-97) and 88% (95% CI, 78-94), respectively. The 2-year and 5-year estimates of DSS were 96% (95% CI, 89-99) and 92% (95% CI, 83-97), respectively (Fig. 1A). The 2-year and 5-year estimates of DFS were 91% (95% CI, 83-96) and 87% (95% CI, 78-93), respectively

Overall survival was significantly lower in patients with T3–4 disease (5-year KM estimate: 69%, 95% CI, 39-86) versus T1–2 disease (5-year KM estimate: 92%, 95% CI, 81-97) ($P = .036$) (Fig. 1B). Likewise, DSS was lower for patients with T3–4 disease (5-year KM estimate: 82%, 95% CI, 53-94) versus T1–2 96%, (5-year KM estimate: 95% CI, 84-99), but this did not reach statistically significance ($P = .07$).

Patients with p16 positive tumors had significantly higher overall survival: 5-year KM estimates 90% (95% CI, 79-96) versus 25% (95% CI, 1-66) ($P < .0001$). DSS was also significantly improved with p16 positivity: 5-year KM estimates 94% (95% CI, 82-98) versus 50% (95% CI, 1-91) ($P = .0078$) (Fig. 1C, D). Interestingly, patients with positive HPV ISH did not have statistically significant differences in OS or DSS.

Univariate analysis was performed to analyze the association of age, gender, tumor site, T stage, N stage, AJCC stage, p16 status, HPV ISH status, smoking, presence of ECS, margin status, and administration of adjuvant chemotherapy or RT with OS and DSS. Tumor stage (T3–4 versus T1–2, hazard ratio [HR] = 2.03; 95% CI, 1.10-3.75), margins (positive vs. negative, HR = 4.78; 95% CI, 1.39-16.42), and p16 status (positive vs. negative, HR = 0.05; 95% CI, 0.012-0.216) significantly impacted overall survival (Table III). Only p16 status was associated with DSS (positive vs. negative, HR = 0.087; 95% CI, 0.01-0.85). Multivariable analysis was then performed to evaluate the association of T stage, margins, and p16 status with OS and DSS. After adjusting for the other variables, p16 status was associated with OS (positive vs. negative, HR = 0.04; 95% CI, 0.01-0.19) and DSS (positive vs. negative, HR = 0.10; 95% CI, 0.01-0.98).

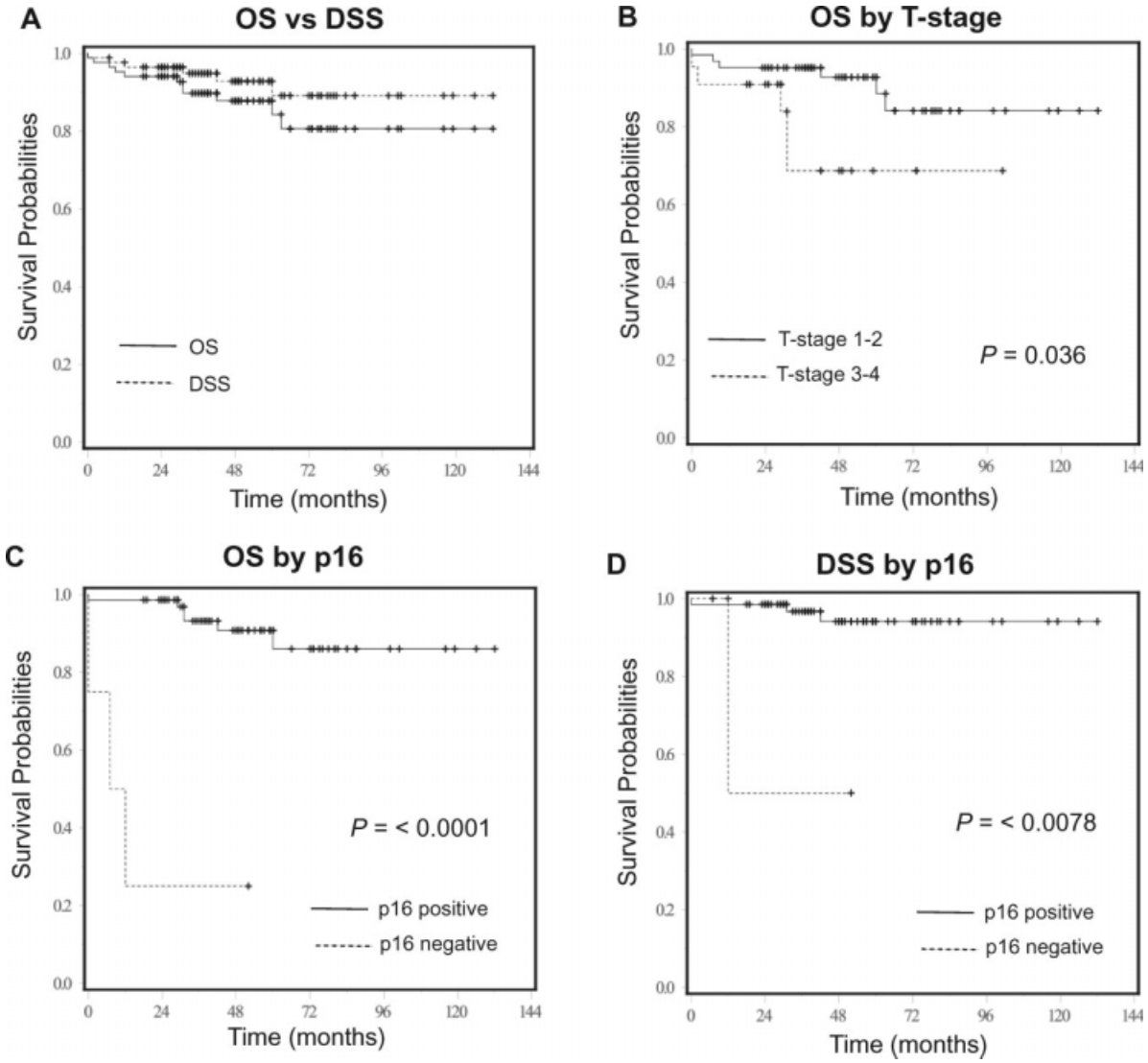

Fig. 1. Kaplan-Meier estimates. (A) OS and DSS for the entire study population. (B) OS by T stage. (C) OS by p16 status. (D) DSS by p16 status. Tick marks represent censored events. OS = overall survival; DSS = disease-specific survival; T stage = tumor stage.

Analysis of Adjuvant Chemotherapy in High-Risk Patients

During the course of this study, a change occurred in tumor board policy from delivering adjuvant RT alone to administering combined adjuvant chemoradiotherapy for treatment of patients with high-risk disease, defined in prior studies as positive margins, two or more positive cervical lymph nodes, or presence of nodal extracapsular spread.[15,16] This policy change allowed for an internal comparison of survival of these high-risk groups according to these two types of adjuvant therapy. Of the patients who met the above high-risk criteria, 45 received adjuvant RT alone and 27 received adjuvant chemoradiotherapy. Within the high-risk RT group, one patient recurred distantly, one recurred regionally and distantly and later developed a second primary, and one developed a second primary. This yields a recurrence rate of 3% (2/45). Within the high-risk adjuvant chemoradiotherapy group, two patients recurred (regional, regional and distant) for a recurrence rate of 7.4% (2/27) (Table IV). The addition of chemotherapy in these patient groups did not statistically affect OS or DSS (Fig. 2).

Locoregional Control Rate and Patterns of Failure

To date, six patients (7%) have had disease progression. One patient (1%) had recurrence at the primary site, four patients (5%) had recurrence in the neck, for an overall locoregional control rate of 94%. Five (6%) patients developed distant metastases. Two of the six patients also developed second primaries (retromolar trigone and contralateral tonsil, respectively) (Table IV).

Swallowing Function

FOSS stages at last follow-up were available for all 84 patients. Eighty-one percent of patients at last follow-

TABLE III.
Univariate and Multivariable Analysis for Overall and Disease-Specific Survival.

Characteristic	Univariate		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall survival				
Age (continuous)	1.02 (0.95-1.09)	.60		
AJCC stage (III vs. IV)	0.52 (0.14-1.97)	.34		
Chemotherapy received (yes vs. no)	1.75 (0.50-6.17)	.38		
ECS (positive vs. negative)	0.92 (0.20-4.24)	.91		
Gender (male vs. female)	0.62 (0.14-2.89)	.55		
ISH HPV (positive vs. negative)	0.48 (0.12-1.96)	.31		
Margin (positive vs. negative)	4.78 (1.39-16.42)	.01	3.83 (0.72-20.50)	.12
N stage (N0–1 vs. N2–3)	0.76 (0.29-1.97)	.57		
p16 (positive vs. negative)	0.05 (0.01-0.22)	<.0001	0.04 (0.01-0.19)	<.0001
RT received (yes vs. no)	0.33 (0.07-1.53)	.16		
Site (BOT vs. tonsil)	1.73 (0.50-5.99)	.38		
Smoking (yes vs. no)	6.83 (0.87-53.37)	.07		
T stage (T3–4 vs. T1–2)	2.03 (1.01-3.75)	.02	1.94 (0.88-4.32)	.10
Disease-specific survival				
Age (continuous)	1.02 (0.93-1.12)	.64		
AJCC stage (III vs. IV)	0.98 (0.11-8.39)	.98		
Chemotherapy received (yes vs. no)	3.19 (0.61-16.71)	.17		
ECS (positive vs. negative)	0.98 (0.12-8.43)	.99		
Gender (male vs. female)	0.28 (0.05-1.54)	.14		
ISH HPV (positive vs. negative)	0.80 (0.08-7.59)	.84		
Margin (positive vs. negative)	4.07 (0.74-22.48)	.11	*	*
N stage (N0–1 vs. N2–3)	2.07 (0.34-12.54)	.43		
p16 (positive vs. negative)	0.087 (0.01-0.85)	.04	0.10 (0.01-0.98)	.05
RT received (yes vs. no)	0.36 (0.04-3.09)	.35		
Site (BOT vs. tonsil)	1.96 (0.36-10.81)	.44		
Smoking (yes vs. no)	*	*		
T stage (T3–4 vs. T1–2)	2.14 (0.93-4.94)	.08	2.00 (0.66-6.07)	.22

*Variable could not be analyzed with Cox proportional model due to absence of events in one or more groups.

HR = hazard ratio; CI = confidence interval; AJCC = American Joint Committee on Cancer; ECS = extracapsular spread; ISH = in situ hybridization; HPV = human papilloma virus; N stage = nodal stage; RT = radiotherapy; T stage = tumor stage; BOT = base of tongue.

up had FOSS stages from 0 to 2, which represents normal to mild dysphagia (Fig. 3A). Thirty-nine patients (46%) had a G-tube placed at some point during treatment of their cancer. Of the 84 patients in the study, 70 patients (83%) progressed through the postoperative recovery period without requiring G-tube placement. The percentage of living patients with G-tubes as a function of time following TLM was plotted (Fig. 3B). The prevalence of patients with G-tubes was 18.8% at 1 year, 9.3% at 2 years, 3.4% at 3 years, 4.7% at 4 years, and 3.8% at 5 years. The greatest number of patients at any given time with G-tubes was 33.7% at 3 months postoperatively, which corresponds to the delivery of adjuvant therapy.

DISCUSSION

This study demonstrates that TLM is a minimally invasive surgical treatment option for advanced oropharyngeal cancer, which with judicious use of adjuvant therapy provides excellent survival and functional outcomes. The role of TLM in this patient cohort was to completely eliminate all known oropharyngeal and neck malignant disease to a negative microscopic margin, such that adjuvant therapy could be directed to areas or patients with pathological markers of high-risk. Thus, TLM was the definitive method of handling the primary disease, and/or directing adjuvant radiation for precisely targeted boosts in the presence of positive margins. The critical role of TLM as apposed to the adjuvant therapy is emphasized by significance of negative margins on survival (H.R. = 4.78).

In the past, advanced oropharyngeal cancer was treated with major open surgery followed by adjuvant RT. Access to the oropharynx often included lip lysis, mandibular osteotomy, and/or transhyoid approaches followed by pharyngectomy or glossectomy (sometimes total) for tumor extirpation. These procedures sometimes resulted in significant morbidity, disfigurement, and swallowing

TABLE IV.
Patterns of Failure and Secondary Primaries.

Patient	Primary Site	T Stage	N Stage	ECS	HPV Positive	Positive Margins	Neck Dissections	High Risk*	Adjuvant Therapy	Site of Recurrence	Time to Recurrence (mo)	Second Primary Site	Time to Second Primary (mo)
1	Tonsil	2	2	Y	Y	N	Ips	Y	RT	D	16		
2	BOT	2	2	Y	?	Y	Ips	Y	RT	R, D	62	Cont. tonsil	43
3	Tonsil	3	1	N	N	N	Ips	N	RT, C	L, R, D	11		
4	BOT	3	3	Y	?	Y	Bil	N†	none	D	1		
5	BOT	2	2	Y	Y	N	Bil	Y	RT, C	R, D	5		
6	BOT	3	2	Y	Y	N	Bil	Y	RT, C	R	24		
7	Tonsil	1	2	Y	Y	N	Ips	Y	RT			RMT	53

*High risk refers to patients with two or more positive nodes, presence of ECS, or positive margins. The critical role of TLM as apposed to the adjuvant therapy is emphasized by significance of negative margins on survival (H.R. = 4.78).
†Patient not included in high-risk analysis due to death prior to adjuvant therapy initiation.
T stage = tumor stage; N stage = nodal stage; ECS = extracapsular spread; HPV = human papilloma virus; Y = yes; N = no; Ips = ipsilateral; RT = radiotherapy; D = distant; BOT = base of tongue; R = regional; cont. = contralateral; C = chemotherapy; L = local; ? = unknown; Bil = bilateral; RMT = retromolar trigone; mo = months.

and speech dysfunction; although with free flap reconstruction, significant functional recovery was possible.[17] According to one study, OS and DSS following these surgeries with adjuvant RT were 52% and 64% at 7 years, respectively.[18]

In 1991 the Veterans Affairs Laryngeal Cancer Study Group, in a trial sponsored by Bristol-Myers Squibb Company (the manufacturer of the chemotherapeutic agents used in that study), showed statistically equivalent survival rates between surgery with adjuvant RT and induction chemotherapy followed by RT for larynx cancer patients.[19] This study generated interest in nonsurgical modalities for advanced head and neck cancer. In 2003 the Radiation Therapy Oncology Group (RTOG) 91-11 study found that concurrent chemoradiation (CCRT) was superior to both induction chemotherapy followed by RT and RT alone for advanced laryngeal cancer.[4] There was, however, no surgical arm for comparison in this study. Furthermore, in absolute terms, both the laryngectomy-free survival (47%) and the overall survival (55%)[20] were modest at 5 years, with a high proportion of severe late toxicity (43% with laryngopharynx dysfunction).[21] Notwithstanding these results, and despite these trials' limitation to advanced laryngeal cancer, CCRT has since been adopted at many centers as a first line treatment of advanced stage cancer for other head and neck subsites, including the oropharynx. To our knowledge, no randomized control trial of surgical versus nonsurgical management of advanced oropharyngeal cancer has been published. It is well known that oropharyngeal cancer has distinct pathophysiology and treatment responses in contrast to laryngeal cancer. Thus, transferring results from laryngeal studies to oropharyngeal cancer carries some risk, especially with the low long-term levels of survivorship, low long-term organ preservation, and high swallowing dysfunction/aspiration risks seen in the larynx studies cited above.[21] Furthermore, it has been shown that at 3 years following diagnosis of recurrence of oropharyngeal disease from failed CCRT and then subsequently treated with surgical salvage, the OS is only 48.5% and DFS is 27%.[22]

Additional published studies for advanced oropharyngeal cancer studies have not included surgical arms,[23–25] and similarly only compared RT with CCRT, and/or trialed neoadjuvant regimens. So it is important to note that CCRT has never been directly compared against surgery plus adjuvant RT in a randomized, prospective, clinical trial. Thus, without evidence, modern surgery for advanced stage oropharyngeal cancer has been relegated to a salvage role at many centers, even though no substantial studies have shown CCRT to offer superior survival to surgery. Five-year overall survival rates for advanced oropharyngeal cancer treated with CCRT hover around a median of 57%.[25–29]

Even though CCRT modalities claim to be "organ preserving" (implying that surgery is not organ preserving), it is important to note in oropharyngeal cancer resection with appropriate reconstruction, that normal swallowing function can be maintained with even up to two thirds of the tongue base removed.[30] Therefore the

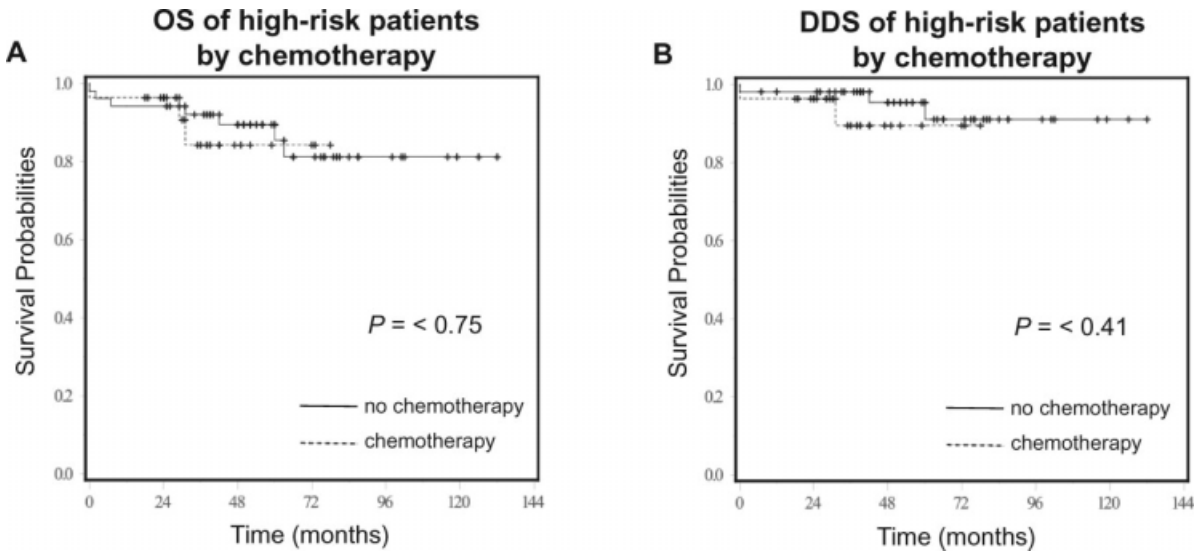

Fig. 2. Kaplan-Meier estimates of high-risk patients. Administration of adjuvant chemotherapy did not affect OS (A) or DSS (B). High risk defined as patients with positive margins, two or more positive cervical lymph nodes, or presence of nodal extracapsular spread. Tick marks represent censored events. OS = overall survival; DSS = disease-specific survival.

emphasis of the term "organ preservation" is difficult to apply to the oropharynx. We believe that in the study of oropharynx cancer, emphasis should be placed on measurement of survival and swallowing function outcomes rather than organ preservation.

Concurrent chemoradiotherapy carries significant morbidity, with grade 3–4 complications being reported in 82% of patients in one study.[25] We show in this study, and others concur,[8] that TLM carries minimal morbidity and provides normal swallowing in nearly all patients postoperatively. In addition, the surgery-related temporary tracheostomy rate was 11% and the mean hospital stay following surgery was 4.3 days, signifying a very low treatment burden and cost.

Studies evaluating CCRT for AJCC stage III and IV oropharyngeal cancer describe 5-year OS ranging from 22% to 74% (median 57%).[25–29] Five-year DSS with CCRT has been reported as 62%.[28] Though direct comparison with these studies cannot be made, our study reports 5-year OS and DSS at 88% and 92%, respectively. The lower rate of T3–4 rate (26%) in our study biases toward improved survival when compared to the average T3–4 rate of 66% in the abovementioned CCRT studies. However, exclusive analysis of only T3–4 disease in our TLM study demonstrates 5-year OS and DSS of 69% and 82%, respectively, which is still favorable compared to the above CCRT studies that include T1–4 disease.

In perusing various published studies of AJCC stage III and IV oropharyngeal cancer, T-stage distribution is commonly demonstrated to be independently prognostic. Therefore, because of different T-stage distributions seen in the CCRT reports above and others,[25,28,31–34] few are comparable, either within that treatment approach or to

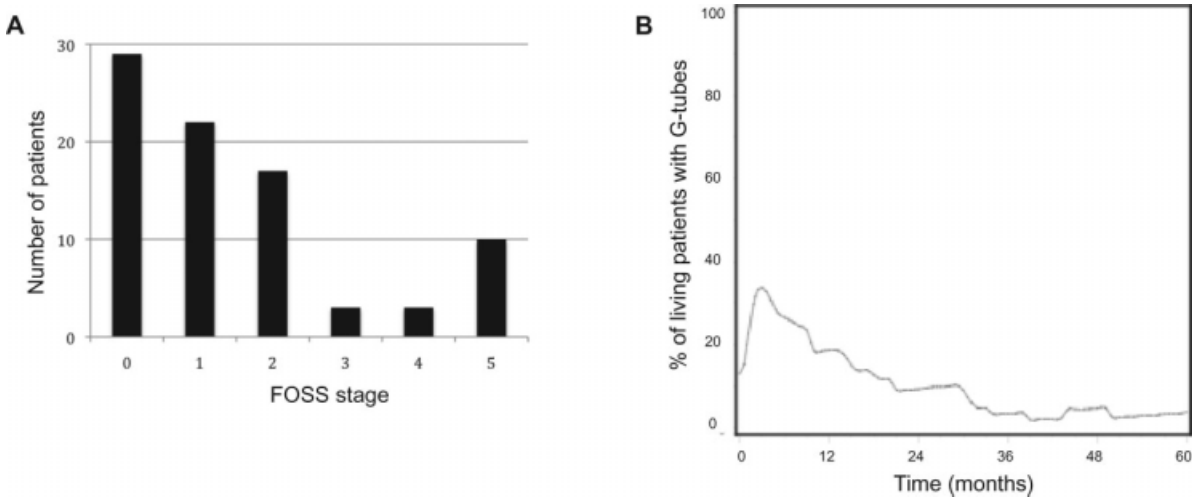

Fig. 3. Functional outcomes following TLM. (A) FOSS by stage. (B) Percentage of living patients with G-tubes as a function of time from surgery. TLM = transoral laser microsurgery; FOSS = Functional Outcome Swallowing Scale; G-tubes = gastrostomy tubes.

TABLE V.
Comparison of Current Study With Huang et al.[29]

	% T Stage 3 or 4	% Locoregional Control	% Overall Survival (3 yr)	% Gastrostomy Tube
Huang, n=71	32*	90	83	35†
Current study, n=84	26	96	91	33 at 3 mo, 3.4 at 3 yr

*Not statistically significant.
†Time following treatment not given.

our study. However, the report by Huang et al.[29] ($n = 71$) shows no significant difference in T-stage distribution from our study population ($p = .46$, Fisher exact test), and it is therefore reasonable to compare these two studies, given the same tumor site and overall stage entry criteria. All their patients were treated with IMRT, concurrent cisplatinum- or carboplatinum-based chemotherapy, and 15 (21%) underwent post-treatment neck dissection. The respective outcomes of the two series are shown in Table V. This comparison shows a higher overall survival, locoregional control rate, and a markedly lower G-tube rate in the currently reported TLM series versus IMRT/CRT with surgery for salvage series. Clearly other variables, such as HPV status and comorbidities, are not reported in the Huang study, so a direct comparison and final conclusions cannot be drawn until a randomized control trial or case matched study can be done. However, from the existing literature, the Huang et al. study is as close as we can come to a comparison report of nonsurgical management.

Regarding our univariate analysis of prognostic factors, we determined, as expected, that positive margins and advanced T stage had a negative impact on overall survival. Some studies have shown that head and neck cancer patients with two or more positive neck nodes, extracapsular spread, or positive margins are at higher risk for recurrence and death.[15] The addition of adjuvant chemoradiotherapy was shown to improve locoregional control in this high-risk patient population.[16,35] Nevertheless, a meta-analysis evaluating the overall role of chemotherapy in head and neck cancer required 16,665 patients to register a 4.4% improvement in survival.[36] Within our study population, extracapsular spread and higher neck nodal stage were not associated with decreased survival. We also found that the addition of adjuvant chemotherapy among high-risk patients in our study did not significantly impact OS or DSS. Many factors, perhaps some immeasurable, might explain these findings; therefore, they should be interpreted with caution, because our study was not designed to evaluate these endpoints. However, taken together, these findings suggest that adding adjuvant chemotherapy, if at all applicable, might be indicated by another yet unknown, nonstandard, high-risk criteria, such as non-HPV related tumors. Our findings therefore generate a valid hypothesis, which would generate a structured study of the question, "Can treatment for high-risk disease be deintensified in the presence of margin-negative TLM resections, and positive biomarkers such as p16?"

Tumor suppressor protein p16 is upregulated by HPV oncogene protein E7.[37] Prior studies report p16 positivity ranging from 32% to 64% in oropharyngeal cancers.[38,39] These same studies also demonstrate statistically improved survival when the p16 biomarker is expressed. Our specimens showed a higher than commonly reported rate of p16 positivity, perhaps because in all analyzed patients, a full surgical resection specimen was available from both the primary site and the neck. Nonsurgical studies are forced to rely on small biopsy samples, which introduce a greater chance of sampling error. We likewise show that p16 positivity independently has a positive impact on both overall and disease-specific survival in univariate and multivariate analyses. It is possible that the high proportion of p16 positive tumors in this study (95%) contribute to our observed high survival rates. We did not find HPV positivity to be associated with survival, as has been reported previously.[40] This may be due to sensitivity discrepancies between different HPV detection techniques (e.g., in situ hybridization vs. polymerase chain reaction). Smith et al. have shown that concurrent expression of p16 and HPV is associated with different survival outcomes than when analyzed separately.[39] This suggests that these biomarkers should be evaluated together, which was not performed in our current study.

Despite being classified as advanced stage due to nodal stage and/or overall AJCC stage, this emerging patient population is showing excellent (treated) survival rates. This apparent survival discrepancy of oropharyngeal cancer patients from other advanced stage head and neck cancer patients is most likely due to the unique pathophysiology of oropharyngeal tumors. Taken together, these data suggest that high-risk criteria, indications for adjuvant therapy (particularly chemotherapy), and AJCC staging for advanced oropharyngeal cancer are worthy of reevaluation. HPV and/or p16 status, positive margins, and tumor stage appear to impact survival, whereas ECS, positive nodes, and AJCC staging are not indicative. Therefore an HPV-derived tumor marker, such as p16 staining is a possible candidate for inclusion in future staging systems, at least for oropharyngeal cancer.

G-tube placement and feedings are often required while treating oropharyngeal cancers. Unfortunately, there are a number of patients that remain G-tube dependent following treatment. G-tube dependence is mainly due to stenosis/fibrosis of the pharyngoesophagus with failure of laryngeal elevation, neuromuscular incoordination, and/or refractory aspiration. This can be caused by surgery, chemoradiation, or a combination of both. This study demonstrates that advanced oropharyngeal cancers can be treated by TLM, with or without adjuvant therapy, and maintain very good swallowing function. Our data shows that 83% of patients remain

G-tube free immediately following resection. The greatest proportion of patients with G-tubes in our study occurred after adjuvant chemoradiotherapy was initiated, suggesting that adjuvant therapy significantly contributed to dysphagia. However, despite this rise during adjuvant therapy, most patients are able to eventually resume oral feeding. Our 3-year post-treatment G-tube rate of 3.4% compares very favorably to the 3-year rates of 18.1% quoted with CCRT.[5]

There are certain limitations with this study that must be considered. First, this is a retrospective analysis of prospectively gathered data. However, recently there has been growing recognition of the prevalence and critical importance of retrospective analysis of prospectively gathered data within the surgical literature, which studies are called "retro-pro."[41] The possibility of selection bias for this treatment cannot be statistically refuted because there is no comprehensive record of how many patients were not eligible for TLM and sent for CCRT or how many patients were not even referred for surgical evaluation. Since 2006, recording measures have been put in place at WUSM to address these issues. The obvious, fully acknowledged, and deliberate selection applied included whether the tumor was resectable by TLM and the knowledge that the patient could safely undergo general anesthesia for approximately 4 hours. Most patients in the study were seen at the WUSM Department of Otolaryngology–Head and Neck Surgery as their first point of referral for definitive treatment, and therefore the latter source of potential bias is possible but less likely. Last, this study reports on cases performed by a single surgeon. Future investigation that combines results of TLM from multiple, experienced, endoscopic surgeons is needed, and is in progress.

CONCLUSION

Transoral laser microsurgery offers a minimally invasive surgical option for complete resection of the primary tumor while maximally preserving healthy, noncancerous tissue. This is achieved by directly visualizing the host-tumor interface under magnified, microscope guidance. Laser resection then allows for precise excision of the tumor. The benefits include focused treatment of the cancer instead of wide field exposure to high levels of RT or systemic chemotherapy, which result in significant injury to surrounding healthy tissues.

This study validates TLM with adjuvant therapy as an effective treatment and function preserving strategy for advanced oropharyngeal cancer, refuting the assumption that all surgery is a morbid method for treatment of advanced oropharyngeal cancer. Higher T-stage, positive margins, and p16 status impacted survival, whereas nodal status, extracapsular spread, and adjuvant chemotherapy did not. Re-evaluation of AJCC staging and high-risk criteria for oropharyngeal cancer is merited. Excellent swallowing function and low G-tube rates were also observed in patients treated with TLM.

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