The Laryngoscope

Long-term Analysis of Transorally Resected p16 + Oropharynx Cancer: Outcomes and Prognostic Factors

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Objective: We observed high survival in a previous report of a p16-positive, oropharyngeal carcinoma (OPC) cohort treated primarily with transoral laser microsurgery (TLM) ± adjuvant therapy and followed for ≥ 12 months. To address long-term outcomes of primary transoral surgery for this unique disease, we present an updated analysis of our cohort with extended follow-up.

Methods: A prospectively assembled TLM cohort of 171 OPC patients was analyzed for disease-free, disease-specific, and overall survival (disease-free survival [DFS], disease-specific survival [DSS], overall survival [OS]) and functional outcomes, with a minimum follow-up of 60 months or to death.

Results: Median follow-up was 103 (60–201) months. Five-year DFS, DSS, and OS estimates were 85% (95% confidence interval [CI]: 80%–91%), 93% (95% CI: 89%–97%), and 90% (95% CI: 86%–95%). Recurrence occurred in 20 (12%; 7 locoregional, 13 distant); median time to recurrence was 18.8 months; and 90% occurred within 48 months. Age, smoking, American Joint Committee on Cancer 8th edition clinical tumor-category, pathologic tumor (pT)-category, pathologic tumor-node-metastasis (pTNM), and any adjuvant were significantly associated with disease-free survival in multivariable analyses, whereas pT-category, pN-category, TNM grouping, and angioinvasion were associated with DSS. A second primary developed in six (3.5%) patients. Indications for gastrostomy were recurrence/second primary (11), postadjuvant esophageal stenosis (6), comorbidities (3), and osteo/chondroradionecrosis (3); only seven (4%) had a gastrostomy tube in the absence of these factors, all of whom received adjuvant therapy. Two had a tracheostomy tube [chondoradionecrosis (1), recurrence (1)].

Conclusion: High 5-year survival and locoregional control were observed, with recurrence occurring more commonly as distant metastasis. The observed time to recurrence suggests posttreatment oncologic surveillance for at least 48 months. Identified prognosticators will inform adjuvant treatment considerations, trial planning, and patient counseling for long-term outcomes.

Key Words: Oropharynx cancer, human papillomavirus, p16 gene, adjuvant therapy, prognosis.

Level of Evidence: 2b

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INTRODUCTION

Human papillomavirus (HPV)-related, p16-positive oropharyngeal squamous cell carcinoma (OPSCC) has been shown as an unique disease entity with improved prognosis compared to p16-negative OPSCC.[1–3] The traditional prognosticators for p16-negative OPSCC are shown to be less impactful in p16-positive OPSCC due to its inherent favorable biology and treatment responsivess.[4–9] Minimally invasive techniques using transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) are commonly employed for the primary treatment of OPSCC.[10–16] Favorable oncologic and functional outcomes with reduced treatment toxicity in p16-positive OPSCC are reported with these minimally invasive techniques in the short term.[11,17,18] However, long-term studies with information on oncologic and functional outcomes or prognosticators for transorally treated p16-positive OPSCC are sparse.[19]

In our institutional study of p16-positive OPSCC cohort treated primarily with TLM and followed for ≥ 12 months, which was published as a Triological Society Candidate Thesis, we observed high disease-free survival of more than 90% and a recurrence rate of 7%.[20] It was not known whether the early excellent oncologic outcomes hold long-term. The functional outcomes of tracheostomy and gastrostomy-tube rates in this cohort were also not known. To address the absence of published data on long-term outcomes and prognosticators for transorally resected cohorts with p16-positive OPSCC, we present our outcomes with a minimum follow-up of 60 months.

MATERIALS AND METHODS

The oncologic outcomes of a prospectively assembled cohort of 171 OPSCC patients treated consecutively with TLM from

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June 1996 through July 2010 was published in a 2012 Triological Thesis by authors B.H.H. and P.S.[20] The institutional human research protection office had approved the TLM database and the research protocol. In the thesis,[20] study patients had a minimum post-TLM follow-up of 12 months. For the current study, follow-up was updated and long-term (≥ 60 months) oncologic outcomes were analyzed, along with functional outcomes of swallowing and airway status. All patients from the original thesis cohort were followed either up to 60 months or to death, whichever occurred first, with none lost to follow-up. Relevant demographic, clinical, tumor, and treatment characteristics were also verified. Importantly, the 8th edition of the American Joint Committee on Cancer (AJCC) stage[21] was used to re-categorize the tumor; the 7th edition of the AJCC was used in the thesis.[20] Details of the eligibility criteria for inclusion, treatment, p16 assessment, follow-up protocol, and study endpoints are provided in the thesis.[20] In brief, previously untreated histologically proven OPC patients receiving TLM and neck dissection ± adjuvant therapy for curative therapy and demonstrating diffuse (nuclear and cytoplasmic) p16-positivity on immunohistochemistry were included. The primary tumor was resected using the basic TLM techniques,[22] and neck dissections were performed simultaneously. The surgical defect healed by secondary intention or was occasionally reconstructed with an acellular graft, local, or free flap as needed. Adjuvant therapy was administered based on high-risk pathologic features such as extracapsular spread (ECS) and positive margins. Factors such as patient preference, and other criteria such as comorbidity and performance status, also impacted adjuvant administration. All patients were followed up with comprehensive clinical examination and imaging as necessary for cancer surveillance.[20] Patients received swallowing rehabilitation with a speech pathologist, as indicated.

Study End Points

The primary endpoint of the study was disease-free survival (DFS). Secondary endpoints were disease-specific survival (DSS), overall survival (OS), and recurrence, as reported previously. Survival definitions are identical to those used in the thesis.[20] The functional outcomes at last follow-up included tracheostomy and gastrostomy rates, as well as Functional Outcome Swallowing Scale (FOSS)[23] scores ranging from 0 to 5, with 0 to 2 being normal/nutritive swallowing, and 4 to 5 being grossly abnormal swallowing requiring a gastrostomy.

Statistical Analysis

The data were analyzed using SPSS 25.0.0 software (IBM Corp., Armonk, NY). Kaplan-Meier analysis was used to compute the survival probability, and survival curves were compared by the log-rank statistic. The association of prognostic variables with DFS and DSS was explored through univariate and multivariate Cox proportional hazard (PH) models; respective hazard ratios (HR) were calculated with 95% confidence intervals (CIs). The PH assumption was assessed using estimated -ln (-ln) survivor curves and Schoenfeld residuals. Multivariable Cox analyses included variables identified as statistically or clinically important. Collinear clinically important variables were evaluated in separate models. The performance of the multivariable model was assessed with c-statistic.[24] A value of 0.5 for the c-statistic denotes no discrimination between patients with and without an event, and 1.0 represents perfect discrimination.

RESULTS

A total of 171 patients were followed for a minimum of 60 months or to death. The median follow-up was 103 months (minimum–maximum = 60.1–201) for the alive cohort, and 98 months (minimum–maximum = 2–201) for the entire cohort. A total of 34 patients (20%) died during the study period. Of these, 16 (9%) had evidence of disease, and 18 (11%) died without disease. Of the 18 patients who died without disease, the cause of death was cardiovascular (5), recurrent pneumonia (4), head and neck second primary (3), progressive Parkinson's disease (2), surgical complications from incarcerated hernia (1) and aortic valve replacement (1), nonhead and neck second primary (1), and skull base osteoradionecrosis (1). Details of cohort selection and characteristics were reported previously.[20] Baseline tumor characteristics by adjuvant treatment type are presented in Table I. The margin status after first TLM resection (Table I) was positive in 14 patients (8%); re-resection was performed in 10, of which eight had no residual tumor. In four of the 14 patients, one refused re-resection or adjuvant, whereas the remaining three received adjuvant chemoradiation.

Survival

The 5-year DFS, DSS, and OS for the overall study were 85% (95% CI: 80%, 91%), 93% (95% CI: 89%, 97%), and 90% (95% CI: 86%, 95%), respectively. The survival outcomes stratified by treatment groups of TLM alone, TLM + radiation, and TLM + chemoradiation are presented in Tables II and III; and Kaplan-Meier estimates are presented in Figures 1 and 2. In patients with recurrence, the median survival after detection of recurrence for patients who died from disease was 17 (0.2–59) months, and for patients who were salvaged and are disease-free was 54 (44–65) months. One patient is alive with disease at 46 months.

Recurrence

Disease recurrence occurred in a total of 20 (12%) patients. The median (minimum–maximum) time to first recurrence was 20.7 months (2.4–58.7 months), with 90% of the recurrences detected within 48 months of TLM (5 within 12 months, 12 within 24 months, 16 within 36 months, 18 within 48 months), whereas two recurred after 48 months. The median (minimum to maximum) time to recurrence was 24 (12–58.7) for local, 8.8 (6.4–28.4) for regional, and 18.8 (2.4–56.9) for distant metastasis. The locoregional recurrence occurred at 27.7 months.

Of the seven patients with locoregional recurrence, three (43%) were in the TLM group and four (57%) were in the TLM + radiation group. Salvage treatment was performed in five patients and palliative/supportive care in two. Three of the seven patients (43%) are alive and disease-free, whereas four died of disease. Of the 13 patients who developed distant metastasis, three (23%) were in the TLM alone group, six (46%) in the TLM + radiation group, and four (31%) in the TLM + chemoradiation group. All patients died of disease, except for one patient who is alive

TABLE I.
Baseline Tumor Characteristics of the Study Cohort Stratified by Treatment Type.

Characteristics	Total (n = 171)	TLM Alone (n = 29, 17%)	TLM + RT (n = 73, 43%)	TLM + CRT (n = 69, 40%)
AJCC 8th cT-category				
1	62 (36)	12 (19)	29 (47)	21 (34)
2	53 (31)	6 (11)	26 (49)	21 (40)
3	32 (19)	8 (25)	11 (34)	13 (41)
4	24 (14)	3 (13)	7 (29)	14 (58)
AJCC 8th pT-category*				
0	8 (5)	2 (25)	2 (25)	4 (50)
1	68 (40)	14 (20)	33 (49)	21 (31)
2	55 (32)	6 (11)	26 (47)	23 (42)
3	26 (15)	6 (23)	8 (31)	12 (46)
4	14 (8)	1 (7)	4 (29)	9 (64)
AJCC 8th cN-category				
N0	15 (9)	11 (73)	3 (20)	1 (7)
N1	122 (71)	15 (12)	62 (51)	45 (37)
N2	16 (9)	3 (19)	2 (13)	11 (69)
N3	18 (11)	0	6 (33)	12 (67)
AJCC 8th pN-category				
N0	17 (10)	13 (77)	3 (18)	1 (6)
N1	127 (74)	15 (12)	60 (47)	52 (41)
N2	27 (16)	1 (4)	10 (37)	16 (59)
AJCC 8th cTNM stage				
I	99 (58)	17 (17)	49 (50)	33 (33)
II	32 (19)	9 (28)	11 (34)	12 (38)
III	40 (23)	3 (8)	13 (33)	24 (60)
AJCC 8th pTNM stage				
I	112 (66)	21 (19)	52 (46)	39 (35)
II	50 (29)	7 (14)	20 (40)	23 (46)
III	9 (5)	1 (11)	1 (1)	7 (78)
Margins				
Negative	157 (92)	26 (17)	69 (44)	62 (39)
Positive	14 (8)	3 (21)	4 (29)	7 (50)
Extracapsular spread				
Present	123 (80)	6 (5)	52 (42)	65 (53)
Absent	31 (20)	10 (32)	18 (58)	3 (10)
Soft tissue metastasis				
Present	78 (51)	3 (5)	30 (38)	45 (58)
Absent	76 (49)	13 (17)	40 (53)	23 (30)
Perineural invasion				
Present	21 (12)	3 (14)	8 (38)	10 (48)
Absent	150 (88)	26 (17)	65 (43)	59 (39)
Angioinvasion				
Present	26 (15)	5 (19)	11 (42)	10 (39)
Absent	127 (74)	22 (17)	50 (39)	55 (43)
Unknown	18 (11)	2 (11)	12 (67)	4 (22)

*Missing pathological T category in 8 cases due to failure to adequately measure tumor size. The cT-category for these 8 cases was T1 (1), T2 (4), T3 (1), T4 (2).

AJCC = American Joint Committee on Cancer; c = clinical; CRT = chemoradiation; p = pathologic; RT = radiation; T = tumor; TLM = transoral laser microsurgery; TNM = tumor, node, metastasis.

with nonprogressive distant metastasis at 46 months. The recurrence site and rates stratified by adjuvant treatment groups are presented in Table III. In the TLM alone group with high-risk features (n = 8), adjuvant was not administered due to refusal with close oncologic surveillance by six patients, refusal of any further management by one, and distant metastasis prior to planned adjuvant initiation in one. Of the six patients with recurrence in the TLM

TABLE II.
Five-Year DFS, DSS, and OS Estimates and Frequency of Outcome Events Stratified by Pathologic TNM Stage and Treatment Type.

Outcome	pTNM	Kaplan-Meier Survival Estimate % (95% confidence intervals); no. of events/no. of patients (%)			
		Overall (n = 171)	TLM alone (n = 29, 17%)	TLM + radiation (n = 73, 43%)	TLM + chemoradiation (n = 69, 40%)
DFS	Stage I	93 (88–98); 15 of 112 (13%)	86 (71–100); 4 of 21 (19%)	92 (85–99); 8 of 52 (15%)	97 (93–100); 3 of 39 (8%)
	Stage II	74 (62–86); 19 of 50 (38%)	43 (6–80); 5 of 7 (71%)	75 (56–94); 6 of 20 (30%)	83 (67–98); 8 of 23 (35%)
	Stage III	56 (23–88); 4 of 9 (44%)	0%; 1 of 1 (100%)*	0%; 1 of 1 (100%)†	71 (38–100); 2 of 7 (29%)
	Overall	85 (80–91); 38 of 171 (22%)	72 (56–89); 10 of 29 (34%)	86 (78–94); 15 of 73 (21%)	90 (83–97); 13 of 69 (19%)
DSS	Stage I	98% (96–100); 5 of 112 (4.5%)	95 (86–100); 1 of 21 (0.8%)	98 (94–100); 4 of 52 (7.6%)	100%; 0 of 39 (0%)
	Stage II	88 (79–97); 7 of 50 (14%)	86 (60–100); 2 of 7 (29%)	85 (69–100); 3 of 20 (15%)	91 (80–100); 2 of 23 (9%)
	Stage III	56 (23–88); 4 of 9 (44%)	0%; 1 of 1 (100%)‡	0%; 1 of 1 (100%)§	71 (38–100); 2 of 7 (29%)
	Overall	93 (89–97); 16 of 171 (9%)	90 (78–100); 4 of 29 (14%)	92 (86–98); 8 of 73 (11%)	94 (89–99); 4 of 69 (6%)
OS	Stage I	96 (93–100); 14 of 112 (12.5%)	91 (78–100); 3 of 21 (14%)	98 (94–100); 8 of 52 (15%)	97 (93–100); 3 of 39 (8%)
	Stage II	82 (71–93); 16 of 50 (32%)	71 (38–100); 4 of 7 (57%)	85 (69–100); 4 of 20 (20%)	83 (67–98); 8 of 23 (35%)
	Stage III	56 (23–88); 4 of 9 (44%)	0%; 1 of 1 (100%)‡	0%; 1 of 1 (100%)§	71 (38–100); 2 of 7 (29%)
	Overall	90 (86–95); 34 of 171 (20%)	83 (69–97); 8 of 29 (27%)	93 (87–99); 13 of 73 (19%)	90 (83–97); 13 of 69 (19%)

*Event at 2.4 months.
†Event at 24 months.
‡Death at 2.6 months.
§Death at 33.6 months.
DFS = disease-free survival; DSS = disease-specific survival; OS = overall survival; p = pathologic; TLM = transoral laser microsurgery; TNM = tumor, node, metastasis.

alone group, four occurred in patients with one or more high-risk features, whereas two occurred in the absence of any high-risk features.

Variables Associated With Survival

Disease-free survival: Age, ever-smoking status, cT3–4 category, pT3–4 category, cN2–3 category, pN2–category, cTNM, pTNM, and angioinvasion were significantly associated with DFS in univariable Cox regression analyses (Table IV). In multivariable analyses, the variables of age (HR 1.04, 95% CI: 1, 1.09, $P = 0.04$), ever-smoking (HR 2.4, 95% CI: 1.09, 5.35, $P = 0.03$), pT3–4 category (HR 3.04, 95% CI: 1.46, 6.32, $P = 0.003$), and any adjuvant therapy (HR 0.37, 95% CI: 0.16, 0.86, $P = 0.02$) were significantly associated with DFS (c-statistic = 0.76, 95% CI: 0.68, 0.84), whereas pN2-category (HR 1.9, 95% CI: 0.78, 4.64, $P = 0.157$) and angioinvasion (HR 1.9, 95% CI: 0.86,4.2, $P = 0.112$) were not. Due to collinearity, the impact of clinical and pathologic T-category, N-category, and TNM staging was assessed through separate models. The pTNM variable was categorized as pTNM II through III versus I due to small number of patients with pTNM stage III, and to reduce the risk of model overfitting in

TABLE III.
Oncologic and Function Outcomes Stratified by Treatment Type.

Outcome	Total (n = 171)	TLM Alone (n = 29, 17%)	TLM + Radiation (n = 73, 43%)	TLM + Chemoradiation (n = 69, 40%)
	n (%)	n (%)	n (%)	n (%)
Survival				
Alive disease-free	136 (79.5)	22 (16)	58 (43)	56 (41)
Alive with disease	1 (0.6)	0	1 (100)	0
Died without disease	18 (11)	4 (22)	6 (28)	9 (50)
Died with disease	16 (9)	4 (25)	8 (50)	4 (25)
Disease recurrence	20 (12)	6 (30)	10 (50)	4 (20)
Local	3 (1.8)	2 (67)	1 (33)	0
Regional	3 (1.8)	0	3 (100)	0
Local and regional	1 (0.6)	1 (100)	0	0
Distant	10 (6)	1 (10)	6 (60)	3 (30)
Regional + distant	3 (1.8)	2 (67)	0	1 (33)
HN second primary	6 (3.5)	2 (33)	2 (33)	2 (33)
Gastrostomy	30 (17%)	3 (10)	12 (40)	15 (50)
Tracheostomy	2 (1%)	1 (50)*	0	1 (50)†

*Developed distant metastasis within 4 weeks of TLM and expired prior to adjuvant therapy initiation.
†Trach-dependent after postchemoradiation laryngeal chondroradionecrosis; HN = head and neck; TLM = transoral laser microsurgery.

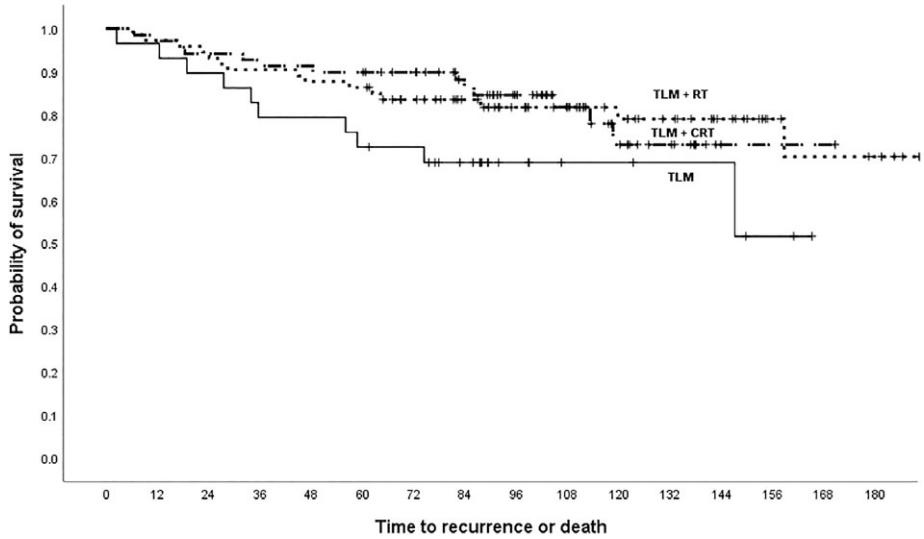

Fig. 1. Disease-free survival Kaplan-Meier estimate stratified by adjuvant treatment type (log rank *P* value = 0.146). CRT = chemoradiation; RT = radiation; TLM = transoral laser microsurgery.

multivariable analyses. The variables of cT3–4 category (HR 3.9, 95% CI: 1.94, 7.89, $P < 0.001$), cTNM (HR 1.8, 95% CI: 1.26, 2.6, $P = 0.002$) and pTNM stage II to III (HR 4.07, 95% CI: 2.03, 8.19, $P = < 0.001$) were also significantly associated with DFS in separate models.

Disease-specific survival: The variables of age, cT3–4 category, pT3–4 category, pN2-category, pTNM, and angioinvasion were significantly associated with DSS in univariable Cox regression analyses. In a multivariable model adjusting for pT3–4 category, pN2-category, angioinvasion, and any adjuvant therapy, pT3–4 category (HR 2.98, 95% CI: 1.07, 8.28, $P = 0.037$), pN2-category (HR 3.76, 95% CI: 1.14, 12.4, $P = 0.030$), and angioinvasion (HR 4.53,95% CI: 1.5, 12.99, $P = 0.005$) were significantly associated with DSS (c-statistic = 0.77, 95% CI: 0.63, 0.91). In a separate model including pTNM to replace pT-category and pN-category, pTNM stage II through III (HR 3.08, 95% CI: 1.01, 9.40, $P = 0.049$) was statistically significant (c-statistic = 0.74, 95% CI: 0.6, 0.88). The cT-category (HR 1.71, 95% CI: 0.59, 4.91, $P = 0.321$), cN-category (HR 1.59, 95% CI: 0.53, 4.83, $P = 0.405$), or cTNM (HR 1.22, 95% CI: 0.69, 2.16, $P = 0.482$) were not significantly associated with DSS.

Functional Outcomes at Last Follow-up

Two (1%) patients had a tracheostomy. Of those, one developed distant metastasis within 4 weeks of TLM, and one developed laryngeal chondroradionecrosis after adjuvant chemoradiation. Thirty (17%) had a gastrostomy tube; indications were disease recurrence/second primary or management thereof (11,6%), posttreatment dysphagia (7,4%), postadjuvant esophageal stenosis (6,4%), medical

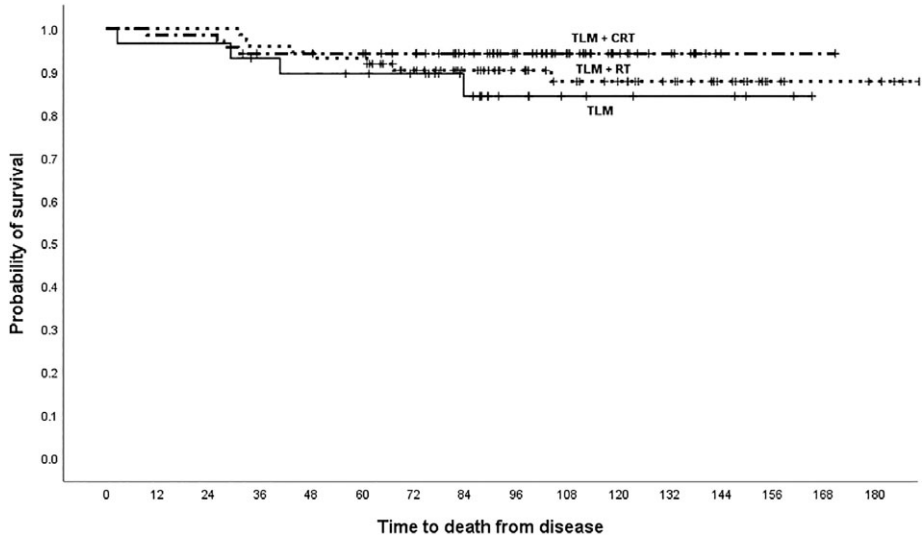

Fig. 2. Disease-specific survival Kaplan-Meier estimate stratified by adjuvant treatment type (log rank *P* value = 0.386). CRT = chemoradiation; RT = radiation; TLM = transoral laser microsurgery.

TABLE IV.
Univariate Cox Proportional Hazard Regression Analysis for Disease-free and Disease-specific Survival.

Variables	Disease-free Survival		Disease-specific Survival	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (continuous)	1.07 (1.03–1.1)	< 0.001	1.05 (1.002–1.11)	0.042
Sex (male vs. female)	0.989 (0.39–2.53)	0.981	0.904 (0.21–3.98)	0.894
Site (tonsil vs. tongue base)	0.89 (0.47–1.68)	0.720	0.706 (0.26–1.89)	0.49
Comorbidity (2–3 vs. 0–1)	0.925 (0.36–2.38)	0.871	0.87 (0.197–3.82)	0.85
Smoking status (ever vs. never)	2.3 (1.12–4.76)	0.023	1.8 (0.63–5.19)	0.274
Smoking (pack years > 10 vs. ≤ 10)	1.60 (0.48–5.31)	0.44	0.84 (0.18–3.91)	0.83
AJCC 8th cT stage (T3–T4 vs. T1–T2)	4.77 (2.42–9.39)	< 0.001	3.0 (1.12–8.07)	0.029
AJCC 8th pT stage (T3–T4 vs. T1–T2)	3.62 (1.82–7.19)	< 0.001	3.91 (1.42–10.77)	0.009
AJCC 8th cN stage N2–3 vs. N0–1	2.14 (1.08–4.25)	0.03	2.61 (0.95–7.17)	0.064
AJCC 8th pN stage N2 vs. N0–1	2.52 (1.21–5.22)	0.013	4.97 (1.85–13.36)	0.001
AJCC 8th cTNM				
II vs. I	3.67 (1.6–8.43)	0.002	2.71 (0.83–8.89)	0.099
III vs. I	3.75 (1.65–8.08)	0.001	2.24 (0.68–7.34)	0.183
AJCC 8th pTNM				
II vs. I	3.58 (1.79–7.15)	< 0.001	3.49 (1.11–11.01)	0.033
III vs. I	6.43 (2.09–19.77)	0.001	13.97 (3.74–52.19)	< 0.001
AJCC 8th pTNM II–III vs. I	3.86 (1.99–7.54)	< 0.001	4.71 (1.64–13.56)	0.004
Margins (positive vs. negative)	2.37 (0.99–5.69)	0.054	2.88 (0.82–10.13)	0.099
Extracapsular spread (yes vs. no)	2.34 (0.71–7.68)	0.162	1.1 (0.31–3.88)	0.878
Soft tissue metastasis (yes vs. no)	1.53 (0.75–3.13)	0.248	1.22 (0.45–3.28)	0.693
Adjuvant therapy				
Radiation vs. none	0.487 (0.22–1.09)	0.08	0.72 (0.22–2.4)	0.594
Chemoradiation vs. none	0.496 (0.22–1.14)	0.098	0.393 (0.1–1.58)	0.188
Adjuvant therapy (any vs. none)	0.49 (0.24–1.01)	0.055	0.564 (0.18–1.75)	0.323
Perineural invasion (yes vs. no)	1.15 (0.45–2.95)	0.769	1.73 (0.49–6.06)	0.394
Angioinvasion (yes vs. no)	2.53 (1.25–5.1)	0.01	5.83 (2.19–15.57)	< 0.001

Significant *P* values presented in boldface.
AJCC = American Joint Committee on Cancer; c = clinical; CI = confidence interval; HR = hazard ratio; p: pathologic; TNM = tumor, node, metastasis.

comorbidities (3,2%), and osteo/chondroradionecrosis (3,2%). The number of patients with a gastrostomy was 17 at 1 year, 18 at 2, 19 at 3, 20 at 4, 21 at 5, 24 at 6, 25 at 7, 28 at 8, 29 at 9, 29 at 10, and 30 at 11 years. The median FOSS score was 1 with a score of 0 in 66 (39%), 1 in 60 (35%), 2 in 12 (7%), 3 in three (2%), 4 in eight (4%), and 5 in 22 (13%) patients. All patients with a FOSS score of 4 or 5 had a gastrostomy tube, for the reasons documented above. Tracheostomy and gastrostomy rates by adjuvant treatment are presented in Table III.

Second Primary

A total of six patients developed a second primary (SP) of the head and neck. Of these, four were p16-positive OPSCC and located in the ipsilateral tonsil in one patient and the contralateral tonsil in three, whereas two were p16-negative located in the hypopharynx. The minimum and maximum time period from TLM for index OPSCC to SP was 36 and 94 months, respectively. Of the four p16-positive OPSCC, one patient (previous TLM + radiation for index OPSCC) died from the SP, three [previous TLM alone (2), TLM + radiation (1) for index OPSCC] are alive and disease-free after TLM resection (2), and TLM + radiation (1). Of the two patients with p16-negative SP (previous TLM + chemoradiation for index OPSCC), one received TLM for posterior hypopharyngeal spindle cell carcinoma but shortly after developed a third primary in the esophagus and died of distant metastasis; the other patient died of local recurrence after pyriform sinus SCC TLM resection.

DISCUSSION

In our p16-positive OPSCC cohort followed for a minimum of 5 years or to death, we observed DFS of 85% and DSS of 93%. Adjuvant therapy was an independent prognosticator for DFS, whereas AJCC 8th tumor stage was for both DFS and DSS. The recurrence rate in the cohort was 12%. A minority of patients had tracheostomy or gastrostomy, mainly due to disease recurrence or morbidity from treatment including adjuvant.

The observed long-term oncologic outcomes in our p16-positive OPSCC cohort have remained as favorable, as in our previously reported thesis.[20] Transoral surgery, including TLM and TORS, has been associated with

better survival for OPSCC.[15,16,25,26] However, long-term outcomes specific to transorally treated p16-positive OPSCC are lacking[27] or come from studies[19,28] with a small number of patients. To our knowledge, no primary transoral studies with both oncologic and functional endpoints are published with minimum 5-year follow-up of living patients; most report outcomes after a minimum follow-up of 12 to 24 months or less.[11,17,18,25,29,30] Melong et al. reported DSS and DFS of 86% and 78% in a cohort of 39 TLM-treated OPSCC patients (23 p16-positive) followed for 36 months. The survival outcomes were not stratified by p16 status, and about 30% of the cohort were postchemoradiation failure recurrences or second primaries.[27] Recurrence occurred in two (9%) patients with HPV-positive OPSCC.[27] Dale et al. evaluated 41 surgically treated HPV-positive OPSCC and observed 5-year OS and DSS estimates of 85% and 91%, respectively, at a mean follow-up of 59.5 months (minimum–maximum, 0–168).[28] No recurrence rates were reported, and the surgical approach was a mix of open resection in 82%, TLM in 10%, and non-TLM transoral resection in 7%.[28] Another study by Hoffmann et al.[19] reported 5-year OS of 83% and DFS of 80% for 48 HPV and p16-positive OPSCC patients at a median follow-up of 72 months. Recurrence occurred in seven (15%) patients with none in the TLM alone group, one distant metastasis in TLM + radiation, and five locoregional + 1 distant metastasis in the TLM + chemoradiation group.[19] The survival from studies by Dale et al.[28] and Hoffmann et al.[19] were similar to our cohort, albeit they had a smaller sample size. The recurrence rate in our long-term (≥ 60 months) cohort is 12%, higher than our previously reported rate of 7%[20] in the same cohort with minimum follow-up of 12 months. The modal pattern of recurrence remains distant metastasis.[20] The time to recurrence varied from 2.4 to 58.7 months, but the majority (90%) of the recurrences occurred within 48 months. We also noted a head and neck second primary rate of 3.5%. A trend toward lower rates of SP tumors has been observed with the growing incidence of HPV-related OPSCC.[31–33] The reduced trend is attributed to the lack of field cancerization effect of tobacco in HPV-related OPSCC[31,33]; however, these patients may have a predilection for a second HPV-related OPSCC. The commonest type of SP in our cohort was another p16-positive OPSCC. The SPs were detected as late as 94 months after the index primary treatment. The outcomes of patients who developed a p16-positive oropharynx SP were better than p16-negative nonoropharyngeal SPs. Based on our results, we observed that the oncologic outcomes after transoral treatment of p16-positive OPSCC are even maintained long-term, but the phenomena of delayed recurrence and SP promote careful and prolonged surveillance of these patients.

In multivariable analyses, the variables of age, smoking, AJCC 8th cT3–4 category, pT3–4 category, pTNM, and any adjuvant therapy were significantly associated with DFS; whereas pT3–4 category, pN2-category, pTNM, and angioinvasion were associated with DSS. These prognostic variables were also identified in our previous report,[20] with the exception of age and the new AJCC 8th staging. The association of age with DFS but not with DSS is expected because DFS includes death from all causes, and medical comorbidities are known to increase with advancing age.[34] The AJCC 7th edition pN-category and TNM-grouping were not prognostic in our previous report,[20] whereas the AJCC 8th edition pathologic tumor, nodal, and TNM-staging are associated with DFS and DSS in the current study. The AJCC 8th edition staging has been shown to improve hazard discrimination and outcome prediction for HPV + OPSCC in several studies,[35–37] and the current study provides further validation; however, as expected from larger multicenter studies,[35,38] the absolute number of pN2 cases is limited. Angioinvasion was prognostic for DSS, whereas perineural invasion, routinely reported ECS (present/absent), and routinely reported soft tissue metastasis (STM) (present/absent) were not associated with reduced DFS or DSS, similar to the thesis.[20] The extent of ECS was not graded for this study; however, in a previous publication[6] that included nearly all patients from the current study cohort, application of ECS grading[39] showed the highest grade of ECS (graded STM) to associate with reduced DFS. Administration of adjuvant therapy associated with improved DFS, and reduced number of recurrences correlative with our recently published matched study by Jackson et al.[16] However, addition of chemotherapy to postoperative radiation did not associate with additional benefit corroborating findings from the thesis[20] and other reports on HPV-related OPSCC,[6,8,40–43] some of which include national cancer database analyses.[40,43] The median (range) adjuvant radiation dose at the primary, ipsilateral, and contralateral neck in our study cohort was 66 (48–70), 66 (36–70), and 56 (45–66) grays (Gy). Treatment deintensification to reduce treatment toxicity while maintaining good oncologic outcomes are underway for both surgical[44–47] and nonsurgical[48,49] management of HPV-related OPSCC. During our study period, institutional deintensification strategies evolved toward eliminating radiation to the primary site in margin-negative resected T1 to T2 tumors,[50] and to the contralateral neck for well-lateralized tumors,[51] as well as reducing the ipsilateral radiation dose to 60 Gy.[52] The current study is limited in its scope to assess treatment deintensification, but we anticipate that transoral surgery with risk-stratified adjuvant therapy will play a relevant role in the future to reduce chemoradiation-related toxicities, including dysphagia[53] in HPV-related OPSCC.[54]

For functional outcomes at a follow-up of ≥ 60 months, we observed a tracheostomy rate of 1% due to indications of recurrence and laryngeal chondroradionecrosis. The swallowing function, as assessed by the FOSS, was normal/nutritive in 83% of the patients. The remaining 17% had a gastrostomy, mainly due to disease recurrence, SP, or post-adjuvant morbidity—including esophageal stenosis and osteo/chondroradionecrosis. In the absence of these factors, a small proportion (4%) was gastrostomy-dependent; all these patients had received a gastrostomy tube in the perioperative period but could not be weaned off after adjuvant completion. Transoral treatment has been associated with decreased rates of posttreatment gastrostomy or tracheostomy for OPSCC[15,25,26,55,56]; however, these rates have been reported at 24 months or less after treatment. Among

studies that included TLM for surgical resection of HPV-related OPSCC and reported survival at 36 months or more, one by Melong et al. reported a 0% gastrostomy rate at 2 years in the absence of recurrent disease,[27] whereas no functional outcomes were reported by Hoffmann et al.[19] or Dale et al.[28] Thus, adequate comparisons of the gastrostomy rate could not be made with previous studies due to the lack of long-term reports for transorally treated p16-positive OSPCC.

We acknowledge the limitation of heterogeneity in the adjuvant therapy type for the study cohort. This heterogeneity is attributed to changes in the adjuvant therapy strategies during the course of the study period (1996–2010) and patient preference, including the refusal to undergo any adjuvant therapy or avoidance of chemotherapy. Similar to the thesis,[20] the current study is limited in making any definitive conclusions about the prognosticators due to the small number of patients experiencing death or disease-recurrence events. Evaluation of large sample size cohorts with mature follow-up in multi-institutional settings will offer more generalizable and conclusive estimates of disease-specific outcomes and prognosticators.

CONCLUSION

High long-term locoregional control of over 95% and disease-free survival of 85% were observed in a p16-positive OPSCC treated with transoral laser resection, neck dissection, and adjuvant therapy (71%), reflecting the generally favorable biology and treatment responsiveness of this unique disease. Adjuvant radiation associated with improved DFS and reduced recurrences. Recurrence, although infrequent, occurred most commonly as distant metastasis. The observed time to recurrence suggests careful posttreatment oncologic surveillance at least for 48 months, the time period during which most of the recurrences occurred. Prognosticators specific to p16-positive OPSCC were identified that may inform future adjuvant treatment considerations, trial planning, and patient counseling for long-term outcomes.

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