Original Article

Surgical Salvage Improves Overall Survival for Patients With HPV-Positive and HPV-Negative Recurrent Locoregional and Distant Metastatic Oropharyngeal Cancer

Theresa Guo, MD[1]; Jesse R. Qualliotine, MD[1]; Patrick K. Ha, MD[1,2]; Joseph A. Califano, MD[1,2]; Young Kim, MD, PhD[1]; John R. Saunders, MD[2]; Ray G. Blanco, MD[2]; Gypsyamber D'Souza, MD[3]; Zhe Zhang, MD[4]; Christine H. Chung, MD[5]; Ana Kiess, MD, PhD[6]; Christine G. Gourin, MD[1]; Wayne Koch, MD[1]; Jeremy D. Richmon, MD[1,2]; Nishant Agrawal, MD[1]; David W. Eisele, MD[1]; and Carole Fakhry, MD, MPH[1,2,3]

BACKGROUND: Human papillomavirus (HPV) tumor status and surgical salvage are associated with improved prognosis for patients with recurrent oropharyngeal squamous cell carcinoma (OPSCC). Current data regarding types of surgery and the impact of surgery for patients with distant metastatic disease are limited. **METHODS:** A retrospective analysis of patients with recurrent OPSCC from 2 institutions between 2000 and 2012 was performed. p16 immunohistochemistry and/or in situ hybridization, as clinically available, were used to determine HPV tumor status. Clinical characteristics, distribution of recurrence site, and treatment modalities were compared by HPV tumor status. Overall survival (OS) was examined using Kaplan-Meier and Cox proportional hazards methods. **RESULTS:** The current study included 108 patients with 65 locoregional and 43 distant metastatic first recurrences. The majority of patients were HPV-positive (80 patients). HPV-positive tumor status was associated with longer time to disease recurrence ($P<.01$). Anatomic site distribution of disease recurrences did not differ by HPV tumor status. HPV-positive tumor status (adjusted HR [aHR], 0.23; 95% confidence interval [95% CI], 0.09-0.58 [$P=.002$]), longer time to disease recurrence (≥1 year; aHR, 0.36; 95% CI, 0.18-0.74 [$P=.006$]), and surgical salvage (aHR, 0.26; 95% CI, 0.12-0.61 [$P=.002$]) were found to be independently associated with OS after disease recurrence. Surgical salvage was independently associated with improved OS compared with nonsurgical treatment among patients with both locoregional (aHR, 0.15; 95% CI, 0.04-0.56 [$P=.005$]) and distant (aHR, 0.19; 95% CI, 0.05-0.75 [$P=.018$]) metastatic disease recurrences. **CONCLUSIONS:** Surgical salvage was found to be associated with improved OS for patients with recurrent locoregional and distant metastatic OPSCC, independent of HPV tumor status. Further prospective data are needed to confirm the role of surgical salvage for distant metastases. ***Cancer*** **2015;121:1977-84.** © *2015 American Cancer Society.*

KEYWORDS: oropharyngeal neoplasms, squamous cell carcinoma of the head and neck, human papillomavirus, salvage therapy, disease recurrence, neoplasm metastasis.

INTRODUCTION

Human papillomavirus (HPV) is responsible for a growing subset of oropharyngeal squamous cell carcinomas (OPSCCs) in the United States and abroad.[1-3] At the time of the primary diagnosis, HPV-positive tumor status is associated with improved response to chemoradiation, progression-free survival, and overall survival (OS).[4,5] Despite improved prognosis, locoregional and distant metastatic recurrences still pose a significant disease burden. Within 3 years of diagnosis, approximately 24% to 27% of patients with HPV-positive OPSCC experience disease recurrence.[5,6]

Although the unique clinical features of HPV-positive OPSCC have been well characterized, few studies have addressed the clinical implications of recurrent disease.[7] Earlier reports have suggested unusual clinical presentations for HPV-associated recurrences.[8-11] Recent prospective data from Radiation Therapy Oncology Group 0129 and 0522 trials demonstrated that site distribution and time to disease recurrence does not differ by HPV tumor status.[12]

Importantly, HPV-positive tumor status[12-14] and receipt of surgical salvage[12] have been shown to be independent markers of improved prognosis among patients with recurrent OPSCC. Although type of disease recurrence (locoregional or distant) was accounted for in the Radiation Therapy Oncology Group analysis, few patients (5 patients) received surgical salvage for distant metastatic disease and details concerning salvage therapies were limited.[12] The study populations in

Corresponding author: Carole Fakhry, MD, MPH, Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University, 6210 JHOC, 601 N. Caroline St, Baltimore, MD 21287-0910; Fax: (410)-614-8610, cfakhry@jhmi.edu

[1]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins Medical Institutions, Baltimore, Maryland; [2]Milton J. Dance, Jr. Head and Neck Center, Greater Baltimore Medical Center, Baltimore, Maryland; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [4]Division of Oncology Biostatistics, Johns Hopkins Medical Institutions, Baltimore, Maryland; [5]Department of Oncology, Johns Hopkins Medical Institutions, Baltimore, Maryland; [6]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medical Institutions, Baltimore, Maryland

DOI: 10.1002/cncr.29323, **Received:** December 12, 2014; **Revised:** January 23, 2015; **Accepted:** January 26, 2015, **Published online** March 17, 2015 in Wiley Online Library (wileyonlinelibrary.com)

the Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) and Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer (SPECTRUM) trials were restricted to patients who were ineligible for surgical or radiation salvage.[13-15] Therefore, we evaluated both surgical and nonsurgical salvage therapies for patients with recurrent locoregional and distant metastatic OPSCC and their prognostic role within the context of HPV tumor status.

MATERIALS AND METHODS

Study Population

The current study was an Institutional Review Board-approved retrospective study of patients treated at Johns Hopkins Hospital and the Greater Baltimore Medical Center between 2000 and 2012. Patients diagnosed with recurrent OPSCC or head and neck squamous cell carcinoma of unknown primary and who had known HPV tumor status were eligible. Unknown primaries were included because these tumors are frequently HPV-related.[16] Disease recurrence was defined as the diagnosis of local, regional, and/or distant disease after the completion of primary treatment with curative intent and a posttreatment disease-free interval of at least 3 months. Patients with second primary tumors or persistent disease (without a disease-free interval) were excluded.

HPV Tumor Status

HPV tumor status was based upon HPV in situ hybridization (105 patients) or p16 immunohistochemistry (94 patients), an established surrogate marker for HPV in OPSCC,[17] at the time of primary diagnosis. HPV tumor status for recurrent lesions was reported based on p16 immunohistochemistry (44 patients) or in situ hybridization (43 patients), as clinically available. Recurrent tumors with discordant HPV tumor status were excluded as second primary tumors (2 patients).[18,19]

Clinical Data

Clinical data were obtained by medical record abstraction. Variables of interest at the time of the primary diagnosis were age, sex, race, history of tobacco and/or alcohol use, TNM stage of disease, and treatment. At the time of first disease recurrence, location of the recurrence (locoregional and/or distant), single or multiple sites of recurrence, anatomic site of distant metastasis, diagnostic method, treatment, and survival data were obtained. Surgical salvage data included surgical procedure, surgical margin status, and length of hospitalization. Surgical margin status was based on the final pathology report. Close surgical margins were considered negative.

The date of disease recurrence was defined by the date of pathologic diagnosis or positron emission tomography imaging if pathology was unavailable. Diagnostic methods of disease recurrence were categorized as clinical examination (at a scheduled appointment), patient symptoms (prompting clinical evaluation), or imaging studies (surveillance studies in the absence of an abnormal examination or symptoms). Anatomic site distribution of distant metastases at first and later recurrences was determined. Time to disease recurrence was defined from the date of the primary diagnosis to the date of first disease recurrence diagnosis.

OS after diagnosis of first disease recurrence was the primary outcome. Additional survival data were also obtained from public social security records for patients for whom the last date of follow-up was before July 2013. Survival analysis was restricted to patients who received treatment for disease recurrence.

Statistical Analysis

Statistical analysis was performed using StataIC12 software (StataCorp LP, College Station, Tex). Chi-square tests were used for categorical data and Wilcoxon rank sum tests were used for comparison of medians. Time to disease recurrence and survival were estimated by the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate survival analyses were performed with Cox proportional hazards regression models. Two-sided P values $<.05$ were considered to be statistically significant. Parsimonious variable selection for the multivariate Cox model was based on clinical and univariate significance. Nonsignificant variables that changed hazard ratios (HRs) by $>10\%$ when removed from the model were also retained.[20]

RESULTS

Patient Characteristics

A total of 108 patients met study criteria (Table 1). The majority of patients were HPV-positive (80 patients; 74.1%). HPV-positive patients were more likely to be white ($P<.01$), male ($P<.01$), and never-smokers ($P=.06$) compared with HPV-negative patients. HPV-positive patients were also more likely to have received nonsurgical primary treatment (83.8% vs 53.6%; $P<.01$).

Patterns of Disease Recurrence

Patterns of disease recurrence were compared by HPV tumor status. HPV tumor status for recurrent disease was available for 45 of 78 HPV-positive patients (57.7%)

TABLE 1. Characteristics of Patients With Recurrent Oropharyngeal Cancer by HPV Tumor Status

	HPV-Positive, N=80, No. (%)	HPV-Negative, N=28, No. (%)	P[a]
Median age at diagnosis y (range)	58 (34-79)	58.5 (30-80)	.95[b]
Race			
White	74 (92.5)	16 (57.1)	<.01
Black	4 (5.0)	11(39.3)	
Other	2 (2.5)	1 (3.6)	
Sex			
Male	70 (87.5)	18 (64.3)	<.01
Female	10 (12.5)	10 (35.7)	
Subsite of primary tumor			
Base of tongue	36 (45.0)	15 (53.6)	.65
Tonsil	35 (43.8)	9 (35.7)	
Unknown primary	4 (5.0)	1 (3.6)	
Other	5 (6.3)	3 (10.7)	
Smoking history at diagnosis			
Ever-smoker	47 (58.8)	22 (78.6)	.06
Never-smoker	33 (41.2)	6 (21.4)	
History of alcohol use at diagnosis[c]			
Yes	30 (37.5)	14 (50)	.25
No	50 (62.5)	14 (50)	
T classification at diagnosis			
T0	4 (5.0)	1 (3.6)	.28
T1	7 (8.7)	7 (25.0)	
T2	24 (30.0)	8 (28.6)	
T3	24 (30.0)	7 (25.0)	
T4	16 (20.0)	5 (17.9)	
Unknown	5 (6.3)	0 (0)	
N classification at diagnosis			
N0-N2a	25 (31.2)	11 (39.3)	.47
N2b-N3	52 (65.0)	17 (60.7)	
Unknown	3 (3.8)	0 (0)	
Overall TNM stage at diagnosis			
I or II	5 (6.3)	4 (14.3)	.22
III or IV	71 (88.8)	24 (85.7)	
Unknown	4 (5.0)	0 (0)	
Primary treatment			.04[d]
Surgery	13 (16.2)	12 (42.9)	.004
Alone	5 (6.2)	3 (10.7)	
With adjuvant	8 (10.0)	9 (32.1)	
Nonsurgical therapy			.91
Primary CRT	61 (76.3)	14 (50.0)	
Radiotherapy only	3 (3.8)	1 (3.6)	
Chemotherapy only	3 (3.8)	1 (3.6)	
Site of first disease recurrence			
Local only	23 (29.5)	8 (28.6)	.83
Regional only	13 (16.7)	4 (14.3)	
Locoregional	15 (19.2)	4 (14.3)	
Locoregional and distant	5 (6.4)	1 (3.6)	
Distant only	22 (28.2)	11 (39.3)	

Abbreviations: CRT, chemoradiotherapy; HPV, human papillomavirus.
[a] Determined using the chi-square test unless otherwise indicated.
[b] Determined using the Wilcoxon rank sum test.
[c] (>2 drinks/d).
[d] Comparing the distribution of all primary treatment modalities overall.

recurrences. There was no difference in the distribution of disease recurrence (local, locoregional, or distant) by HPV tumor status (Table 1). Similar percentages of HPV-positive and HPV-negative patients had local (29.5% vs 28.6%; $P = .93$), locoregional (35.9% vs 28.6%; $P = .48$), and distant metastatic (34.6% vs 42.8%; $P = .44$) disease at the time of first recurrence (Table 1). Twelve patients had multiple sites of disease at the time of first recurrence, and the distribution was similar for HPV-positive and HPV-negative patients (11.5% vs 12.0%; $P = .91$)

TABLE 2. Patterns of Distant Metastatic Disease[a]

Anatomic Site	HPV-Positive n=43 No. (%)	HPV-Negative n=14 No. (%)	P
Lung	30 (69.7)	7 (50.0)	.41
Mediastinal/hilar lymph nodes	5 (11.6)	3 (21.4)	
Bone	5 (11.6)	3 (21.4)	
Skin/dermal	2 (4.6)	2 (14.3)	
Liver	6 (13.9)	1 (7.1)	
Brain	4 (9.3)	1 (7.1)	
Thyroid	2 (4.6)	1 (7.1)	
Adrenal	0 (0)	1 (7.1)	

Abbreviation: HPV, human papillomavirus.
[a] In the follow-up period.

Among patients with any history of distant metastases (57 patients), the lung was the most common site for both HPV-positive and HPV-negative patients ($P = .18$) (Table 2). Mediastinal lymph nodes were the second most common site of distant disease recurrence, followed by bone and skin. The distribution of distant metastatic sites did not differ by HPV tumor status ($P = .41$).

Treatment of Disease Recurrence

The majority of patients received treatment at the time of initial disease recurrence (Table 3). Surgical salvage was the most common treatment (61 patients; 61.6%) and frequently administered with adjuvant radiation (42 patients; 68.9%). Nonsurgical treatment (33 patients) consisted of chemotherapy (45.5%), radiotherapy (24.2%), and chemoradiation (30.3%), and did not differ by HPV tumor status (Table 3).

Patients receiving surgical salvage did not differ with regard to age (median age of 56 years vs 58 years; $P = .28$) or primary treatment modality ($P = .64$). However, a greater percentage of patients who underwent surgical salvage were free of disease for $\geq$1 year compared with patients who received nonsurgical treatment (75.4% vs 54.5%; $P = .038$). For patients with distant metastatic disease recurrence (38 patients), surgical salvage was also associated with a longer disease-free interval ($P = .016$). Patients with multiple sites of disease were more likely to receive nonsurgical treatment compared with patients with a single disease site (80.0% vs 29.8%; $P = .002$).

Details of surgical procedures were available for all 61 patients who underwent surgical salvage for locoregional or

TABLE 3. Treatment of Disease Recurrence[a]

	HPV-Positive N=78 No. (%)	HPV-Negative N=28 No. (%)	*P*
Any salvage therapy			.12
Yes	72 (92.3%)	22 (78.6%)	
No	3 (3.8)	2 (7.1)	
Unknown	3 (3.8)	4 (14.2)	
Surgical salvage[b]			
Yes	49 (68.1)	12 (54.5)	.25
No	23 (31.9)	10 (45.5)	
Surgery only	16 (32.7)	2 (16.7)	.28
Surgery and adjuvant therapy	33 (67.3)	10 (83.3)	
Nonsurgical salvage			
Chemotherapy only	9 (39.1)	6 (60.0)	.25
Radiotherapy only	5 (21.7)	3 (30.0)	
CRT	9 (39.1)	1 (10.0)	

Abbreviations: CRT, chemoradiotherapy; HPV, human papillomavirus.
[a] Two patients with metastatic disease at the time of the primary diagnosis were excluded.
[b] Of 94 patients who received treatment.

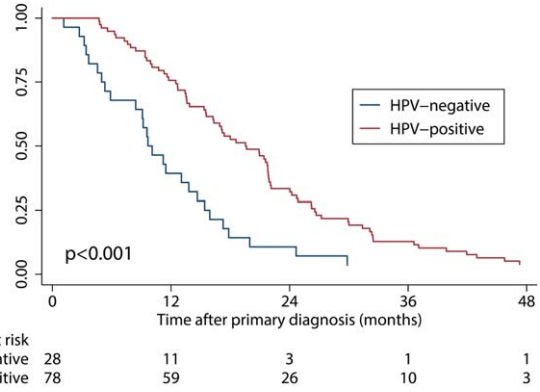

Figure 1. Time to disease recurrence from the time of primary diagnosis of oropharyngeal cancer compared according to human papillomavirus (HPV) tumor status.

distant metastatic disease recurrence. Surgical salvage for locoregional recurrence (46 of 61 patients; 75.4%) included wide local excision with or without neck dissection (29 patients, including transoral robotic surgery in 4 patients), total laryngectomy with or without total glossectomy (7 patients), and neck dissection only (10 patients). Of these 46 locoregional salvage surgeries, 21 (45.7%) were extensive enough to require tracheostomy (13 patients), placement of a gastrostomy tube (9 patients), and/or free flap reconstruction (14 patients). The average postoperative length of stay was 6.5 days (42 patients; range, 0-28 days). There was no difference in prevalence of positive surgical margins (42 patients) by HPV tumor status (34.3% vs 30.0%; $P = .80$).

Surgical salvage for distant metastasis was performed for 16 patients, 14 of whom were HPV-positive. These procedures were predominantly pulmonary resections (9 of 16 patients; 56.3%), 7 of which (77.8%) were video-assisted thoracoscopic surgeries and 3 of which (33.3%) were for multiple lung nodules. Four patients underwent mediastinal lymphadenectomy, including 3 with concomitant pulmonary resections. Additional procedures included craniotomy, dermal excision, hepatectomy, and laminectomy. The average length of stay was 3.8 days (11 patients; range, 1-9 days).

Time to Disease Recurrence

Diagnosis of disease recurrence was significantly later for HPV-positive patients than HPV-negative patients (median time to disease recurrence, 19.6 months vs 9.9 months; $P<.001$) (Fig. 1). In Kaplan-Meier analysis, HPV-positive patients were found to have an increased time to disease recurrence for both locoregional ($P = .07$) and distant ($P<.001$) metastatic recurrence. In multivariate analysis, HPV-positive tumor status was independently associated with longer time to disease recurrence (adjusted HR [aHR], 0.39; 95% confidence interval [95% CI], 0.23-0.68 [$P = .001$]). Factors at primary diagnosis that were not associated with time to disease recurrence included age, sex, race, smoking and alcohol history, tumor stage, lymph node stage, and primary treatment modality ($P>.10$).

A majority of recurrences occurred within 2 years after the primary diagnosis for both HPV-positive patients (66.0%; 95% CI, 55.4%-76.3%) and HPV-negative patients (89.3%; 95% CI, 74.9%-97.3%). The method of diagnosis of disease recurrence differed by HPV tumor status ($P = .02$). HPV-positive recurrences were primarily diagnosed by imaging (47.4%), whereas clinical examination was the main method of diagnosis for HPV-negative recurrences (46.4%). Distant metastatic disease was more likely than locoregional disease to be diagnosed by imaging (73.7% vs 24.2%; $P<.001$). The method of diagnosis was not associated with the time to disease recurrence ($P = .46$).

Survival Analysis

The median follow-up time after disease recurrence was 15.8 months (range, 0.2-105.8 months). HPV-positive patients had significantly improved OS after recurrence compared with HPV-negative patients (3-year OS 55.7% vs 25.2%; $P = .01$) (Fig. 2A). Median survival was longer for HPV-positive patients compared with HPV-negative patients (82.6 months vs 23.1 months).

Factors associated with OS after disease recurrence on univariate analysis included time to recurrence ($\geq$1

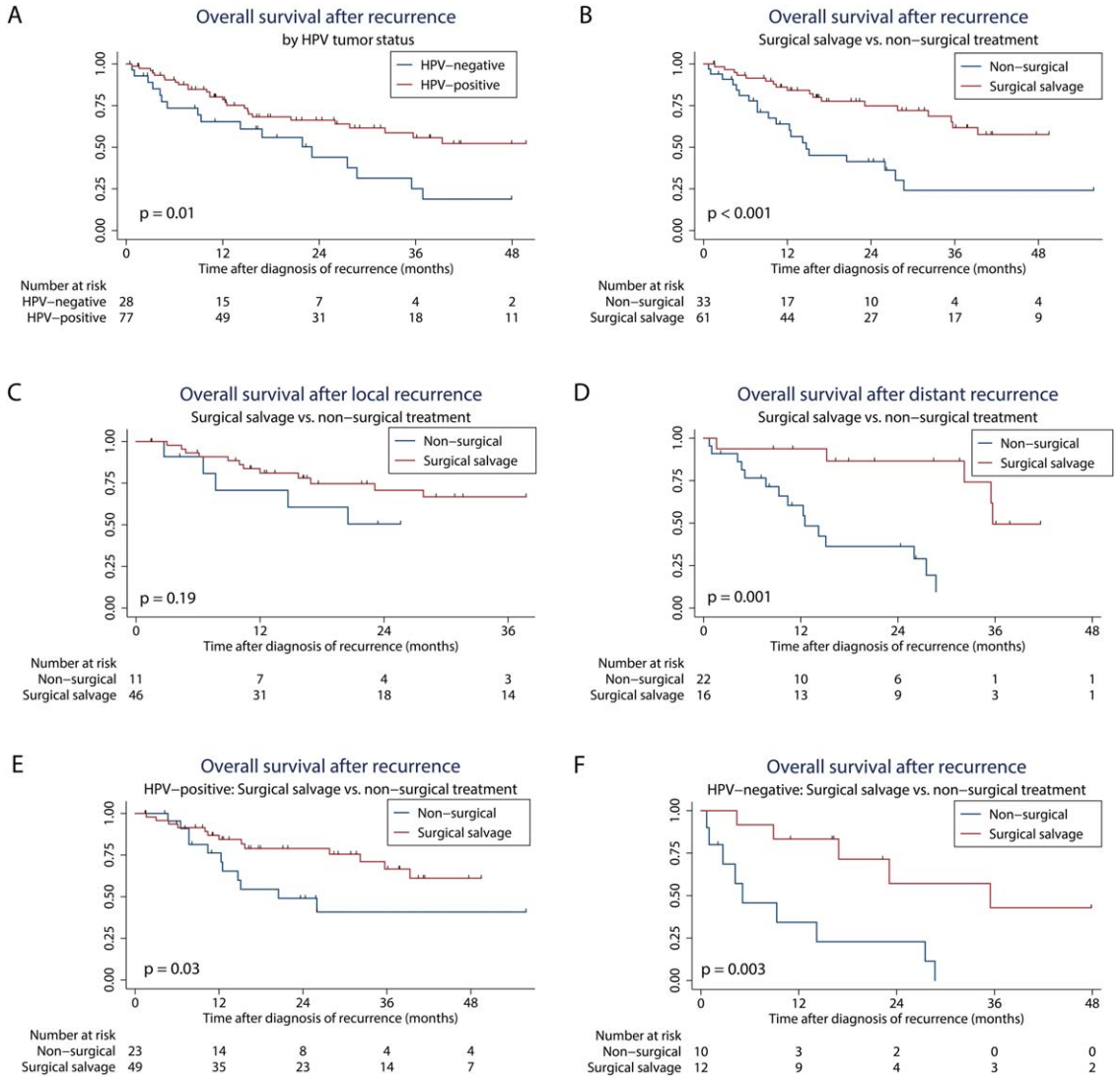

Figure 2. Kaplan-Meier curves demonstrating overall survival (OS) after disease recurrence. Censored patients are denoted by a tick mark. (A) OS after disease recurrence by human papillomavirus (HPV) tumor status (comparing HPV-positive versus HPV-negative patients). The 2-year OS was 66.3% (95% confidence interval [95% CI], 53.2%-76.5%) versus 44.0% (95% CI, 22.6%-63.6%) and the 3-year OS was 55.7% (95% CI, 41.0%-68.2%) versus 25.2% (95% CI, 8.4%-46.3%). (B) OS after disease recurrence by salvage therapy (comparing surgical versus non-surgical salvage). The 2-year OS rate was 74.9% (95% CI, 60.2%-84.8%) versus 41.4% (95% CI, 23.3%-58.6%) and the 3-year OS was 61.8% (95% CI, 44.6%-75.1%) versus 24.1% (95% CI, 8.8%-43.6%). (C) OS after locoregional disease recurrence by salvage therapy (comparing surgical versus non-surgical salvage). The 2-year OS was 70.7% (95% CI, 52.6%-83.0%) versus 50.5% (95% CI, 18.7%-75.7%) and the 3-year OS was 66.8% (95% CI, 48.0%-80.1%) versus 50.5% (95% CI, 18.7%-75.7%).(D) OS after distant disease recurrence by salvage therapy (comparing surgical versus non-surgical salvage). The 2-year OS was 86.5% (95% CI, 55.8%-96.5%) versus 36.3% (95% CI, 15.5%-57.7%) and the 3-year OS was 49.5% (95% CI, 16.0%-76.3%) versus 9.7% (95% CI, 0.7%-33.5%). (E) OS after disease recurrence by salvage therapy (comparing surgical versus non-surgical salvage) for patients with HPV-positive disease. The 2-year OS was 78.9% (95% CI, 63.2%-88.5%) versus 49.0% (95% CI, 25.8%-68.8%) and the 3-year OS was 66.6% (95% CI, 47.2%-80.3%) versus 40.9% (95% CI, 18.0%-62.6%). (F) OS after disease recurrence by salvage therapy (comparing surgical versus non-surgical salvage) for patients with HPV-negative disease. The 2-year OS was 57.1% (95% CI, 20.1%-82.3%) versus 22.9% (95% CI, 3.5%-52.2%) and the 3-year OS was 42.9% (95% CI, 10.8%-72.4%) and the 3-year OS could not be assessed for the nonsurgical group.

year; HR, 0.41; 95% CI, 0.23-0.73 [$P = .002$]), HPV-positive tumor status (HR, 0.47; 95% CI, 0.26-0.88 [$P = .02$]), multiple sites of disease recurrence (HR, 3.22; 95% CI, 1.53-6.79 [$P = .002$]), and treatment with surgical salvage (HR, 0.32; 95% CI, 0.17-0.60 [$P < .001$]) (Fig. 2B). Locoregional recurrence was associated with a nonsignificant reduction in risk of death compared with distant recurrence (HR, 0.57; 95% CI, 0.31-1.02

[$P = .055$]). All other variables were not associated with OS (age, sex, race, smoking history, initial lymph node status, and primary treatment modality; $P > .10$).

Patients who underwent surgical salvage had significantly improved OS compared with patients who received nonsurgical treatment for disease recurrence (3-year OS rate: 61.8% vs 24.1%; $P < .001$) (Fig. 2B). The median survival time was 101.5 months for patients who underwent salvage surgery and 14.7 months for those who received nonsurgical treatment.

Patients with locoregional disease recurrence who were treated with surgical salvage had a nonsignificant improvement in survival compared with those who received nonsurgical treatment ($P = .19$) (Fig. 2C). However, surgical salvage was associated with improved survival in patients with distant metastatic recurrence ($P = .001$) (Fig. 2D). The median survival for patients with distant metastatic disease who underwent surgical salvage was 35.7 months compared with 12.5 months for patients who received nonsurgical treatment.

Surgical salvage improved OS for both HPV-positive patients ($P = .03$) (Fig. 2E) and HPV-negative patients ($P = .003$) (Fig. 2F) compared with nonsurgical treatment. For patients with distant metastatic recurrence, surgical salvage was associated with improved OS for both HPV-positive patients ($P = .03$) and HPV-negative patients ($P = .05$), although the number of HPV-negative patients in this group was limited (11 patients).

In multivariate analysis, HPV-positive tumor status (aHR, 0.23; $P = .002$), longer time to disease recurrence ($\geq$1 year; aHR, 0.36; $P = .006$), primary surgical treatment (aHR, 0.21; $P = .007$), and treatment with surgical salvage (aHR, 0.26; $P = .002$) were each independently associated with improved OS (Table 4). When patients were stratified by type of disease recurrence, surgical salvage was found to be independently associated with improved survival for both locoregional (aHR, 0.15; 95% CI, 0.04-0.56 [$P = .005$]) and distant (aHR, 0.19; 95% CI, 0.05-0.75 [$P = .018$]) metastatic disease recurrence.

TABLE 4. Multivariate Analysis of Factors Associated With OS After Disease Recurrence[a]

Variable	HR (95% CI)	*P*
HPV tumor status (positive vs negative)	0.23 (0.09-0.58)	.002
Age at diagnosis, (per year)	1.04 (0.99-1.09)	.062
Race (white vs nonwhite[b])	0.57 (0.23-1.44)	.24
Smoking history (ever vs never)	0.72 (0.33-1.61)	.43
Initial lymph node classification (N stage 2b-3 vs 0-2a)	0.91 (0.35-1.61)	.84
Time to disease recurrence ($\geq$1 y vs <1 y)	0.36 (0.18-0.74)	.006
Site of disease recurrence (locoregional vs distant)	2.31 (0.83 −6.39)	.11
No. of disease recurrences (multiple vs single)	3.27 (1.07-10.01)	.038
Primary treatment (surgical vs nonsurgical)	0.21 (0.066-0.65)	.007
Salvage treatment (surgical vs nonsurgical)	0.26 (0.12-0.61)	.002

Abbreviations: 95% CI, 95% confidence interval; HR, adjusted hazard ratio; HPV, human papillomavirus; OS, overall survival.
[a] Restricted to those patients who received salvage therapy with complete data (92 patients).
[b] Black and other race.

DISCUSSION

The results of this study suggest a robust survival advantage associated with surgical salvage for patients with recurrent OPSCC, even for those with distant metastatic disease. Until recently,[12] recurrent OPSCC was associated with poor OS, and the role of salvage surgery, especially among patients with distant metastatic disease, was questioned within the context of this relatively poor OS and high potential morbidity.[21-23] Previous studies on surgical salvage of recurrent OPSCC focused primarily on locoregional disease recurrence and did not account for HPV tumor status.[22,24-26] In this analysis, OS was evaluated after locoregional and distant metastatic recurrence within the context of HPV tumor status and salvage therapy.

Surgical salvage therapy for the oropharynx has traditionally been associated with increased morbidity such as gastrostomy tube dependence[27] and the need for a midline mandibulotomy. However, the landscape of recurrent OPSCC is changing with the rise of HPV-related disease,[1,2] as well as advancements in surgical approaches to the oropharynx. Transoral robotic surgery has become a viable option for select patients with recurrent OPSCC, with decreased reported morbidity including shorter hospital stays, improved margin control, and decreased tracheostomies and gastrostomy tubes.[28] Based on the extent of recurrent disease, minimally invasive surgery for locoregional disease may not always be possible. It was not used in the majority of locoregional recurrences reviewed herein (4 patients), and thus improvement in OS associated with salvage surgery was likely not dependent on minimally invasive techniques.

Salvage surgery for distant metastatic disease extended the median OS from 12.5 months to 35 months. This reduction in the risk of death remained significant after adjustment for HPV tumor status, age, time to disease recurrence, and multiple sites of disease recurrence (aHR, 0.19; $P = .018$). Surgery for metastatic disease was primarily performed for patients with lung metastases. As observed in this study cohort, minimally invasive pulmonary procedures are also now widely

available.[29] An important consideration that was not captured by the current analysis is the quality of life after salvage surgery for distant metastatic disease.

Surgery for metastatic disease poses a departure from the traditional management of metastatic disease in patients with head and neck cancer. Only the chemotherapeutic treatment of distant metastases is supported by strong level 1 evidence within the current National Comprehensive Cancer Network (NCCN) guidelines.[30] Although surgical salvage for distant metastases is an option for patients with good performance status and limited distant disease, evidence for nonchemotherapy treatments are based on lower-level 2A evidence and data defining surgically appropriate distant metastases are lacking.[30] In cancers occurring in other anatomic sites such as the colorectum, NCCN guidelines have integrated site-specific recommendations for the surgical resection of liver and pulmonary metastases based on an established body of evidence.[31-35] Nonsurgical approaches for the localized treatment of metastatic disease (eg, radiosurgery) are frequently used for distant metastases and also warrant further investigation. The current study results in the context of current guidelines underscore the need to prospectively collect analogous surgical and nonsurgical salvage data to elucidate the potential role of surgery and radiotherapy in the treatment of patients with distant metastatic OPSCC to inform future guidelines.

Surgical salvage was associated with improved survival for patients with both HPV-positive and HPV-negative disease, although this survival advantage was more prominent in those with HPV-negative disease. Patients with HPV-positive disease recurrence may be more responsive to salvage chemotherapy treatments,[14] thereby attenuating the survival advantage of surgical salvage. To our knowledge, few studies to date have characterized the impact of HPV tumor status on recurrent OPSCC.[13,14,36] The data from the current study are consistent with recent observations that HPV-positive patients who develop disease recurrence retain an HPV-positive clinical phenotype including race and smoking history, and do not resemble HPV-negative patients.[12] In concordance with recent literature, anatomic site distribution of disease recurrences did not differ by HPV tumor status.[12]

In this cohort, HPV-positive tumor status was associated with a longer time to disease recurrence. These data are consistent with previous reports that the majority of failures, regardless of HPV tumor status, occur within 2 years.[12,37] Differences in time to disease recurrence may be explained by frequent posttreatment imaging in clinical trial protocols, which could expedite the diagnosis of HPV-positive recurrences. By contrast, fewer than one-half of recurrences (43%) in this study cohort were diagnosed with imaging studies, the majority of which were HPV-positive (80.4%). It is interesting to note that a longer time to disease recurrence was found to be independently associated with a significant reduction in the risk of death. To the best of our knowledge, this finding has not been reported previously within the context of HPV tumor status.[27] Further studies will elucidate the role of HPV tumor status on the timing of disease recurrence and its implications with regard to the intensity of posttreatment surveillance in the clinical practice setting.

A limitation of the current study is that HPV tumor status was classified based upon tumor status of primary disease rather than disease recurrence. A majority of HPV-positive patients (45 of 78 patients; 57.7%) had HPV tumor status available for disease recurrence. However, previous studies have shown that among patients with prior HPV-positive OPSCC, recurrent disease is HPV-positive in 92% to 97% of cases, including pulmonary recurrences.[18,19]

The primary limitations of the current study are biases inherent to retrospective analyses. In particular, there are potential selection biases that remain unaccounted for, including patient and physician preferences, comorbidities, performance status, and extent of recurrent disease. A prospective study would be necessary to ascertain the rationale for treatment choices and patient eligibility or ineligibility for treatment. Furthermore, the complications and morbidity associated with these treatments could be reliably characterized with prospective data collection. Additional biases may include tertiary institutional referral patterns and nonuniform clinical practices both at the time of primary diagnosis and at disease recurrence. Future prospective studies of the surgical treatment of patients with recurrent and distant metastatic OPSCC will elucidate these relevant clinical questions.

Patients with recurrent OPSCC should be counseled regarding the potential survival advantages of surgical salvage, regardless of HPV tumor status or site of disease recurrence (locoregional or distant). HPV tumor status remains an important prognostic marker in the setting of disease recurrence. These data argue for the inclusion of HPV tumor status and receipt of surgical salvage in the design and analyses of clinical trials. The independent survival advantage of surgical salvage in patients with distant metastatic disease highlights the need to prospectively collect data to inform future NCCN guidelines with higher levels of evidence than currently available.

FUNDING SUPPORT

Supported by grants P50DE019032 and 2T32DC000027-26, the Milton J. Dance Jr. Head and Neck Center and Oral Cancer Foundation.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26:612-619.
2. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29:4294-4301.
3. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356:1944-1956.
4. Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst*. 2008;100:261-269.
5. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med*. 2010;363:24-35.
6. Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol*. 2014;32:2940-2950.
7. Pfister DG, Fury MG. New chapter in our understanding of human papillomavirus-related head and neck cancer. *J Clin Oncol*. 2014;32:3349-3352.
8. Huang SH, Perez-Ordonez B, Liu FF, et al. Atypical clinical behavior of p16-confirmed HPV-related oropharyngeal squamous cell carcinoma treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;82:276-283.
9. Huang SH, Perez-Ordonez B, Weinreb I, et al. Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral Oncol*. 2013;49:79-85.
10. Ruzevick J, Olivi A, Westra WH. Metastatic squamous cell carcinoma to the brain: an unrecognized pattern of distant spread in patients with HPV-related head and neck cancer. *J Neurooncol*. 2013;112:449-454.
11. Muller S, Khuri FR, Kono SA, Beitler JJ, Shin DM, Saba NF. HPV positive squamous cell carcinoma of the oropharynx. Are we observing an unusual pattern of metastases? *Head Neck Pathol*. 2012;6:336-344.
12. Fakhry C, Zhang Q, Nguyen-Tan PF, et al. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. *J Clin Oncol*. 2014;32:3365-3373.
13. Argiris A, Li S, Ghebremichael M, et al. Prognostic significance of human papillomavirus in recurrent or metastatic head and neck cancer: an analysis of Eastern Cooperative Oncology Group trials. *Ann Oncol*. 2014;25:1410-1416.
14. Vermorken JB, Psyrri A, Mesia R, et al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. *Ann Oncol*. 2014;25:801-807.
15. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359:1116-1127.
16. El-Mofty SK, Zhang MQ, Davila RM. Histologic identification of human papillomavirus (HPV)-related squamous cell carcinoma in cervical lymph nodes: a reliable predictor of the site of an occult head and neck primary carcinoma. *Head Neck Pathol*. 2008;2:163-168.
17. Begum S, Gillison ML, Ansari-Lari MA, Shah K, Westra WH. Detection of human papillomavirus in cervical lymph nodes: a highly effective strategy for localizing site of tumor origin. *Clin Cancer Res*. 2003;9:6469-6475.
18. Bishop JA, Ogawa T, Chang X, et al. HPV analysis in distinguishing second primary tumors from lung metastases in patients with head and neck squamous cell carcinoma. *Am J Surg Pathol*. 2012;36:142-148.
19. Vainshtein J, McHugh JB, Spector ME, et al. Human papillomavirus-related oropharyngeal cancer: HPV and p16 status in the recurrent versus parent tumor. *Head Neck*. 2015;37:8-11.
20. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993;138:923-936.
21. Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope*. 2000;110(3 pt 2 suppl 93):1-18.
22. Zafereo ME, Hanasono MM, Rosenthal DI, et al. The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer*. 2009;115:5723-5733.
23. Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. *Head Neck*. 2014;36:144-151.
24. Kano S, Homma A, Hayashi R, et al. Salvage surgery for recurrent oropharyngeal cancer after chemoradiotherapy. *Int J Clin Oncol*. 2013;18:817-823.
25. Nichols AC, Kneuertz PJ, Deschler DG, et al. Surgical salvage of the oropharynx after failure of organ-sparing therapy. *Head Neck*. 2011;33:516-524.
26. Matoscevic K, Graf N, Pezier TF, Huber GF. Success of salvage treatment: a critical appraisal of salvage rates for different subsites of HNSCC. *Otolaryngol Head Neck Surg*. 2014;151:454-461.
27. Kostrzewa JP, Lancaster WP, Iseli TA, Desmond RA, Carroll WR, Rosenthal EL. Outcomes of salvage surgery with free flap reconstruction for recurrent oral and oropharyngeal cancer. *Laryngoscope*. 2010;120:267-272.
28. White H, Ford S, Bush B, et al. Salvage surgery for recurrent cancers of the oropharynx: comparing TORS with standard open surgical approaches. *JAMA Otolaryngol Head Neck Surg*. 2013;139:773-778.
29. Nakajima J, Takamoto S, Tanaka M, Takeuchi E, Murakawa T, Fukami T. Thoracoscopic surgery and conventional open thoracotomy in metastatic lung cancer. *Surg Endosc*. 2001;15:849-853.
30. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancer. Version 2.2014. Available at: nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed October 6, 2014.
31. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg*. 2004;239:818-825; discussion 825-827.
32. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol*. 1997;15:938-946.
33. Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. *Chest*. 2001;119:1069-1072.
34. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. Version 2.2015. Available at: nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed October 7, 2014.
35. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Rectal Cancer. Version 1.2015. Available at: nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed October 7, 2014.
36. Psyrri A, Rampias T, Vermorken JB. The current and future impact of human papillomavirus on treatment of squamous cell carcinoma of the head and neck. *Ann Oncol*. 2014;25:2101-2115.
37. Trosman S A-KS, Koyfman SA, et al. Distant metastatic failure patterns in squamous cell cancer of the oropharynx (SCCOP) treated with chemoradiation: the impact of human papillomavirus (HPV). *Int J Radiat Oncol Biol Phys*. 2014;88:471.