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ORIGINAL ARTICLE – HEAD AND NECK ONCOLOGY

Transoral Resection of Human Papillomavirus (HPV)-Positive Squamous Cell Carcinoma of the Oropharynx: Outcomes with and Without Adjuvant Therapy

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ABSTRACT

Background. With the rise of oropharyngeal squamous cell carcinoma associated with human papillomavirus (HPV), appropriate treatment strategies continue to be tailored toward minimizing treatment while preserving oncologic outcomes. This study aimed to compare the outcomes for those undergoing transoral resection with or without adjuvant therapy for HPV-related oropharyngeal carcinoma.

Methods. A case-match cohort analysis was performed at two institutions on patients with HPV-related oropharyngeal squamous cell carcinoma. All the subjects underwent transoral surgery and neck dissection. The patients treated with surgery alone were matched 1:1 to those treated with surgery and adjuvant therapy using two groups identified as confounders: T-stage (T1/2 or T3/4) and number of pathologically positive lymph nodes ($\leq$4 or >4).

Results. The study identified 105 matched pairs, with a median follow-up period of 42 months (range 3.1–102.3 months). The patients were staged as T1/T2 (86%) or T3/4 (14%). Each group had five patients with more than four positive lymph nodes. Adjuvant therapy significantly improved disease-free survival (hazard ratio [HR] 0.067; 95% confidence interval [CI] 0.01–0.62) and was associated with a lower risk of local and regional recurrence (risk ratio [RR] 0.096; 95% CI 0.02–0.47). No difference in disease-specific survival (HR 0.22; 95% CI 0.02–2.57) or overall survival (HR 0.18; 95% CI 0.01–2.4) was observed with the addition of adjuvant therapy. The risk of the gastrostomy tube was higher for those receiving adjuvant therapy (RR 7.3; 95% CI 2.6–20.6).

Conclusions. Transoral surgery is an effective approach for the treatment of HPV-related oropharyngeal carcinoma. The addition of adjuvant therapy appears to decrease the risk of recurrence and improve disease-free survival but may not significantly improve overall survival.

Oropharyngeal squamous cell carcinoma (OPSCCa) associated with the human papilloma virus (HPV) continues to rise.[1] With the rise of HPV-related OPSCCa, appropriate treatment strategies continue to be tailored toward minimizing the intensity of treatment while preserving oncologic outcomes. Currently, patients with HPV-positive OPSCCa are treated on the basis of recommendations similar to those for HPV-negative disease although these two patient populations have a very different prognosis. The oncologic outcomes for patients with HPV-related OPSCCa tend to be very favorable, which has led to deintensification of treatment regimens.

The two main treatment options for OPSCCa endorsed by the National Comprehensive Cancer Network (NCCN) guidelines are surgery with or without adjuvant therapy and radiation with or without chemotherapy.[2] The favorable survival seen with HPV-related OPSCCa has been demonstrated with both treatment approaches.[3] At a time

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when younger and healthier patients are undergoing treatment for cancer with favorable survival, the choice of treatment becomes even more imperative because the treatment toxicities will have an even greater impact on long-term quality of life. The goal to decrease treatment morbidity while maintaining oncologic outcomes has led to the gain in popularity of transoral surgery.

Transoral robotic surgery (TORS) and transoral laser microsurgery (TLM) offer a minimally invasive approach to the oropharynx with similar oncologic outcomes and lower postoperative morbidity than traditional open approaches.[4] These surgical techniques have provided a viable treatment option that has oncologic outcomes comparable with those for radiation-based approaches and also have provided an additional means of deintensification.[5,6] Patients undergoing transoral surgery for HPV-related OPSCCa have low recurrence rates at the primary site and regional nodal basin.[7,8] Despite this, these patients often are recommended to undergo adjuvant treatment in the primary setting.

This study therefore aimed to evaluate the oncologic outcomes for patients with HPV-related oropharyngeal carcinoma undergoing surgery alone in a case-matched analysis compared with the outcomes for those undergoing surgery with adjuvant therapy. The study also aimed to determine factors related to locoregional recurrence and the success rates for salvage treatments. We hypothesized that patients undergoing transoral surgery with neck dissection alone have a higher risk of locoregional recurrence but that this does have an impact on overall survival or disease-specific survival secondary to successful salvage.

MATERIALS AND METHODS

Institutional review board approval was granted from both study centers: Washington University School of Medicine and Mayo Clinic–Rochester. Data on all consecutive patients undergoing transoral resection of HPV-positive OPSCCa at the two academic centers between January 2007 and November 2013 were retrospectively collected.

Patients were identified in the transoral surgery databases maintained at each respective institution. Only patients with pathologically proven HPV-positive OPSCCa from the palatine tonsil or tongue base treated with transoral surgery and neck dissection were included in the study. The patients in the adjuvant therapy group must have completed all recommended radiation or chemoradiation to be included. Disease related to HPV was determined by p16 immunohistochemistry. Transoral surgery consisted of either TORS or TLM for the primary tumor, with selective neck dissection of the involved and high-risk nodal basins. Recommendations for adjuvant therapy were based on multidisciplinary discussion with radiation and medical oncology. For the group undergoing surgery alone, adjuvant therapy was withheld based on these discussions or patient preferences.

All the patients were clinically staged with physical examination, computed tomography (CT), or magnetic resonance imaging (MRI) of the neck; CT of the chest; and positron emission tomography (PET)/CT scan at the discretion of the treating physician. All tumors were confirmed to be HPV-related squamous cell carcinoma by testing for p16-positivity on immunohistochemistry and staged pathologically from the surgical specimen according to the American Joint Committee on Cancer Staging Manual, 7th edition.[9] Locoregional recurrences were determined to be on the date of biopsy or imaging if the patient did not undergo biopsy.

Because pathologic T stage and number of positive lymph nodes are known confounders of treatment impact on survival,[10,11] patients undergoing surgery alone were matched 1:1 by T stage (T1/2 or T3/4) and number of pathologically positive lymph nodes ($\leq$4 or >4) with those undergoing surgery with adjuvant therapy. Matching was performed using the SAS statistical software package (SAS 9.4; SAS Institute Inc., Cary, NC, USA). If a case had more than one match, only one case was randomly selected for a matched pair.

Smoking status in the respective databases was classified as "current smoker" if the patient was actively smoking at the time of presentation, "former smoker" if the patient had at least a 10-pack-per-year history but was no longer smoking at the time of presentation, or "nonsmoker" if the patient was not smoking at the time of presentation and did not have a 10-pack-per-year history. Smoking status then was dichotomized for statistical analysis to include "smokers" (current and former smokers) and "nonsmokers."

Statistical Analysis

Descriptive statistics were used to describe the distribution of characteristics in each of the two study groups. Bivariate analysis using paired-samples *t* test for continuous level variables and McNemar's test for categorical variables was used to explore for significant differences in the distribution of each study variable between the two matched cohorts. Univariable stratified Cox PH regression analysis was used to investigate the association and impact of each variable with overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) in the setting of matched cohorts and multivariable Cox regression used to assess the impact of adjuvant therapy on survival after control for confounding. Date of surgery was

defined as time zero for the analysis. Conditional Poisson regressions were used to estimate associations of the variables with recurrence and gastrostomy tube placement. Conditional Poisson regression is the appropriate method for risk estimation in the setting of matched-pair cohort data.[12,13] Variables significantly associated with each of the outcomes listed in the univariable analysis (evaluated at an alpha level of 0.05) were included in the multivariable analysis. For statistical analysis, STATA 12.0 (StataCorp 2011, Stata Statistical Software: Release 12; Statacorp LP, College Station, TX, USA) was used.

RESULTS

This study identified 105 matched pairs of patients (174 men and 36 women) with a mean age of 62 ± 9.8 years. The median follow-up period was 42 months (range 3.1–102.3 months). Of the 105 patients who received adjuvant treatment, 43 had radiation and 62 had radiation and chemotherapy. The clinical and pathologic characteristics of the matched-pair groups are summarized in Table 1.

The 5-year estimated OS rate was 89% (95% confidence interval [CI] 81–97%) for those treated with surgery alone and 90% (95% CI 82–98%) for those receiving adjuvant therapy. The distribution of recurrences in each treatment group is summarized in Table 2. Kaplan–Meier estimates of OS, DSS, and DFS for each treatment group are shown in Fig. 1. Adjuvant therapy resulted in a significantly increased DFS but no significant difference in OS or DSS.

Uni- and multivariable analyses are shown in Table 3. After control was used for age and smoking status, adjuvant therapy was associated with a decreased risk of recurrence (risk ratio [RR] 0.096; 95% CI 0.02–0.47). After control was used for age and smoking, adjuvant therapy was associated with a decreased risk of recurrence (DFS) (hazard ratio [HR] 0.067; 95% CI 0.01–0.62). No difference in DSS (adjusted hazard ratio [aHR] 0.22; 95% CI 0.02–2.57) or OS (aHR 0.18; 95% CI 0.01–2.40) was observed with the addition of adjuvant therapy. The risk of the gastrostomy tube was greater for those receiving adjuvant therapy (RR 7.3; 95% CI 2.6–20.6; $p < 0.001$).

Margins were positive in three patients. Neither of the two patients receiving adjuvant therapy for positive margins had a recurrence during follow-up periods of 40 and 53 months, respectively. In the surgery-alone group, one patient had a local recurrence 12 months after a positive margin. He refused re-resection of the original margin as well as any additional therapy and ultimately died of disease 17 months after the recurrence.

A recurrence was experienced by 12% of the patients ($n = 26/210$) at a median of 9 months (range

TABLE 1 Clinical and pathologic characteristics

	Surgery ($n = 105$) *n* (%)	Surgery + adjuvant ($n = 105$) *n* (%)	Percentage difference (95% CI)
Mean age	63 ± 10.7	61 ± 8.6	2.5 (0.04 to 0.91)[a]
Gender			
Male	84 (80)	90 (86)	6 (−4 to 16)
Female	21 (20)	15 (14)	
Center			
1	47 (45)	46 (44)	–1 (−14 to 12)
2	58 (55)	59 (56)	
Smoking			
No	63 (60)	46 (44)	–16 (−29 to −3)
Yes	42 (40)	59 (56)	
ACE-27			
None	53 (53)	52 (50)	3 (−10 to 17)
Mild	31 (31)	42 (40)	−11 (−24 to 2)
Moderate + severe	16 (16)	11 (10)	6 (−14 to 12)
Subsite			
BOT	42 (40)	41 (39)	−1 (−14 to 12)
Tonsil	62 (60)	64 (61)	
Treatment			
Surgery alone	105	–	NA
Adjuvant radiation	–	43 (41)	
Adjuvant chemoradiation	–	62 (59)	
ECE			
No	81 (77)	35 (33)	−44 (−56 to 32)
Yes	24 (23)	70 (67)	
PNI			
No	100 (95)	93 (89)	−6 (−13 to 1)
Yes	5 (5)	12 (11)	
LVI			
No	93 (89)	85 (81)	−8 (−18 to 2)
Yes	12 (11)	20 (19)	
Margins			
Negative	104 (99)	103 (98)	−1 (−4 to 2)
Positive	1 (1)	2 (2)	
Pathologic T stage			
1 and 2	90 (86)	90 (86)	NA
3 and 4	15 (14)	15 (14)	
Lymph node			
≤4	100 (95)	100 (95)	NA
>4	5 (5)	5 (5)	

CI confidence interval, *ACE-27* Adult Comorbidity Evaluation-27, *BOT* base of tongue, *ECE* extracapsular extension, *PNI* perineural invasion, *LVI* lymphovascular invasion, *NA* not applicable

[a] Mean difference and 95% CI

TABLE 2 Recurrence characteristics

	Surgery only ($n = 105$) *n* (%)	Surgery + adjuvant ($n = 105$) *n* (%)	Percentage difference (95% CI)
Recurrence			
No	82 (78)	102 (97)	19 (10 to 28)
Yes	23 (22)	3 (3)	
Local			
No	96 (91)	103 (98)	7 (0.9 to 13)
Yes	9 (9)	2 (2)	
Regional			
No	90 (86)	105 (100)	14 (7 to 21)
Yes	15 (14)	0 (0)	
Distant			
No	103 (98)	104 (99)	1 (–2 to 4)
Yes	2 (2)	1 (1)	

CI confidence interval

1–59 months). The characteristics of the patients with a recurrence and salvage therapy are shown in Table 4. The patients receiving adjuvant therapy experienced three recurrences (3%; 2 local and 1 distant). The local recurrence of one patient was successfully salvaged with radiation and chemotherapy. The remaining two patients died of disease. The surgery-alone patients experienced 23 recurrences (22%). Those with indications for recommended adjuvant therapy such as T3–4, N2+ nodal disease, or extracapsular extension (ECE) had a recurrence rate of 24% compared with 20% for those with no such features. Six of the nine local recurrences were successfully salvaged. Two of the patients died of disease, and one patient had not been followed up after completion of salvage chemoradiation therapy.

Of the 15 regional recurrences, three occurred in the contralateral untreated neck in the surgery-alone group. All three patients had primary tonsil cancers. All three were successfully salvaged by neck dissection, with one patient receiving adjuvant radiation therapy. One of these patients ultimately died of distant metastasis but had no further regional recurrence.

Of those six surgery-alone patients who died of disease, two had distant metastases, one had concomitant breast cancer metastases in cervical lymph nodes, and one had positive surgical margins but refused re-resection, adjuvant therapy, and salvage therapy. The remaining two patients died of locoregional disease.

DISCUSSION

Our multi-institutional matched analysis for transorally resected HPV-related OPSCCa showed that addition of adjuvant therapy for surgical patients was associated with lower risk of disease recurrence. Although adjuvant therapy lowered the risk of local and regional recurrence, no difference in distant spread was observed. Distant metastasis is a major mode of failure in HPV-related OPSCCa.[11,14,15] The risk for distant metastasis did not seem to be determined by the primary treatment and likely will continue to be a source of treatment failure.

The addition of adjuvant therapy resulted in a significantly improved DFS but no observed improvement in DSS or OS. This is likely secondary to the success of available surgery, radiation, and chemotherapy as salvage methods.

As the treatment of HPV-related OPSCCa moves toward deintensification, it is prudent to understand the reasons why we add therapy and why outcomes of individual treatment methods become critically important. This is particularly pertinent because the findings in this study and other series[16] show that the addition of postoperative adjuvant therapy is associated with significant increases in swallowing-related morbidity. Very few reports specifically describe analysis of the oncologic outcomes and treatment failures for patients with HPV-related OPSCCa treated with definitive surgery alone.

Grant et al.[17] evaluated 69 patients who underwent TLM with or without neck dissection and found excellent disease control and low morbidity with primary transoral surgery. These authors did not specifically address HPV-related disease. Funk et al.[18] evaluated 25 patients undergoing surgery alone with intermediate- to high-risk features that would have qualified them for adjuvant therapy. They found a 20% recurrence rate at a median of 4.8 months after surgery. For two of the five patients who had recurrence, the recurrence was in the contralateral, untreated

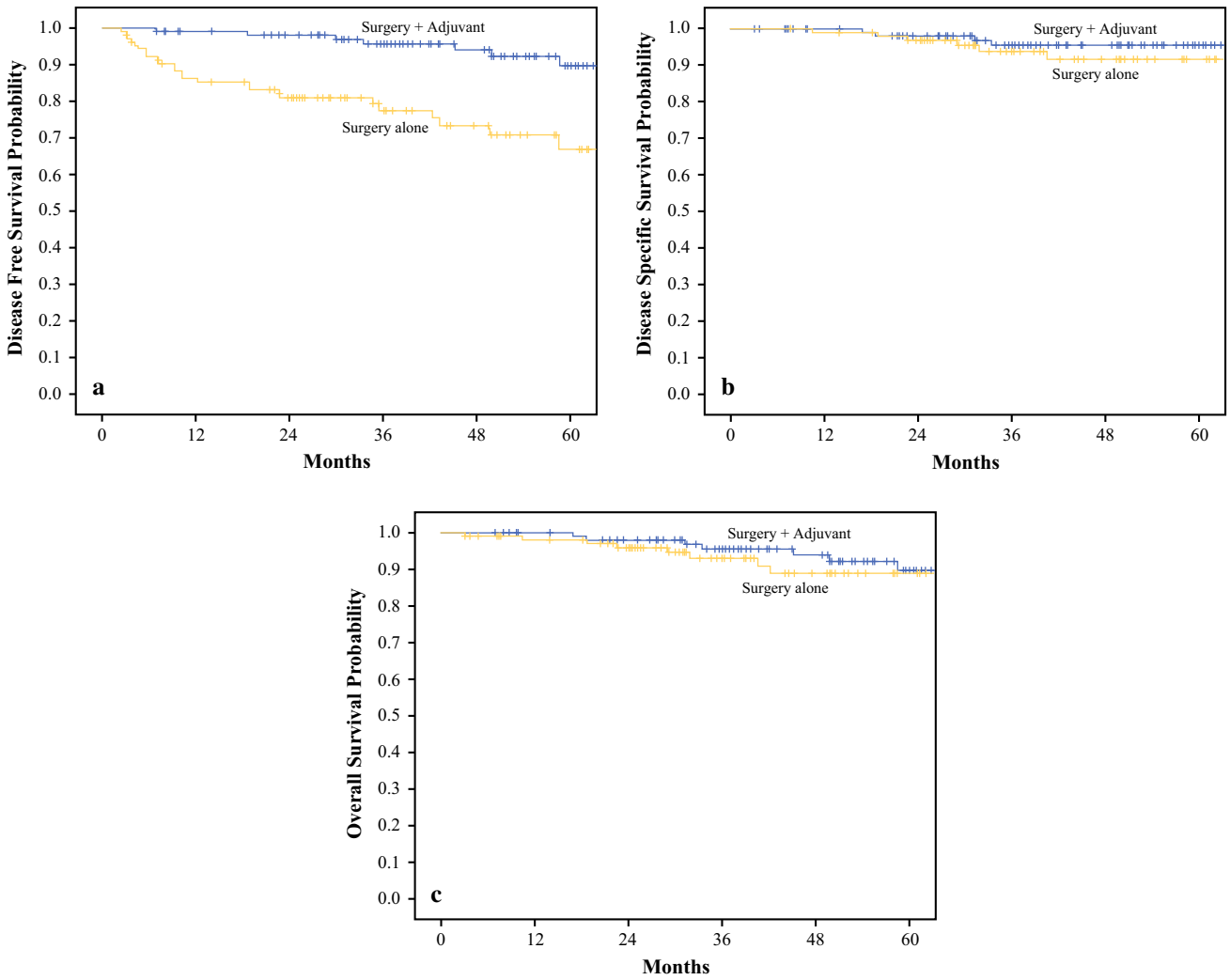

FIG. 1 Kaplan–Meier estimates of survival after surgery with and without adjuvant therapy. **a** Disease-free survival. **b** Disease-specific survival. **c** Overall survival

neck. All five patients were successfully salvaged with multimodality therapy and are alive at this writing with no evidence of disease 17 to 23 months after salvage treatment. In the current study, three patients had recurrence in the contralateral neck, and all were successfully salvaged at the nodal basin.

The amount of adjuvant therapy, mainly the addition of chemotherapy, for patients undergoing transoral surgery also remains controversial. The presence of ECE and positive surgical margins are considered high-risk features and indicators for adjuvant chemoradiation therapy as recommended by the NCCN.[19] In a critical appraisal of the literature used to establish the NCCN guidelines, Sinha et al.[16] concluded that the guidelines for recommending adjuvant chemotherapy in addition to radiation therapy are not based on high-level evidence and that its role remains unknown in surgically treated HPV-related OPSCCa. This conclusion is supported by multiple studies that have not identified ECE as a risk factor for survival in surgically managed, HPV-related OPSCC.[10,20–24] The role of tobacco exposure in HPV-positive versus HPV-negative disease also is not well understood. These controversies are likely a product of the better prognosis for patients with HPV-related OPSCCa than for those with HPV-negative disease.

As a result, no consensus currently exists on the optimum management of HPV-related OPSCCa. This is partly because clinicians do not consistently agree on prognostic features. Studies have demonstrated that the prognosis and related factors for HPV-related OPSCCa differ from those for HPV-negative disease and that conventional prognostic features do not predict treatment outcomes.[10,11,15,20,21,25] Most recently, Kaczmar et al.[15] described 114 patients treated with TORS and did not identify conventional poor prognostic variables as predictors of treatment failure. Sinha et al.[10] reported that more than four metastatic lymph

TABLE 3 Uni- and multivariable analysis of outcomes

	Recurrence RR (95% CI)	DFS HR (95% CI)	DSS HR (95% CI)	OS HR (95% CI)
Univariable				
Age	1.02 (0.96–1.09)	1.03 (0.97–1.09)	1.01 (0.93–1.10)	1.04 (0.97–1.12)
Center	0.75 (0.26–2.16)	2.25 (0.69–7.30)	0.67 (0.11–3.99)	1.67 (0.39–6.97)
Smoking	0.58 (0.23–1.48)	0.80 (0.32–2.03)	1.5 (0.25–8.98)	1.33 (0.29–5.96)
ACE-27				
Mild	1.28 (0.42–3.89)	0.85 (0.21–3.41)	0.78 (0.08–7.12)	0.66 (0.07–6.01)
Moderate + severe	1.54 (0.30–7.87)	1.86 (0.41–8.42)	1.29 (0.14–11.84)	1.52 (0.17–13.92)
Subsite (tonsil vs. BOT)	0.33 (0.03–3.20)	0.50 (0.05–5.51)	1	1
ECE	0.5 (0.15–1.66)	0.63 (0.20–1.91)	1.0 (0.14–7.10)	0.75 (0.17–3.35)
PNI	0.75 (0.17–3.35)	1 (0.25–4.00)	2.0 (0.18–22.06)	2.0 (0.18–22.1)
LVI	1.0 (0.29–3.45)	0.71 (0.27–3.25)	1.0 (0.14–7.10)	0.75 (0.17–3.35)
Margins	0.50 (0.07–3.71)	0.62 (0.08–4.56)	0.19 (0.02–1.50)	0.243 (0.03–1.87)
Path T stage (1 and 2 vs. 3 and 4)	NA	NA	NA	NA
Lymph node ($\leq$4 vs. >4)	NA	NA	NA	NA
Adjuvant therapy	0.07 (0.02–0.31)	0.19 (0.08–0.43)	0.48 (0.14–1.63)	0.50 (0.19–1.29)
Multivariable				
Age	0.96 (0.86–1.07)	0.97 (0.89–1.05)	0.98 (0.88–1.09)	0.99 (0.91–1.1)
Smoking	1.28 (0.27–6.16)	4.41 (0.43–45.03)	4.22 (0.26–67.32)	5.63 (0.35–89.67)
Adjuvant therapy	0.096 (0.02–0.47)	0.067 (0.01–0.62)	0.22 (0.02–2.57)	0.18 (0.01–2.4)

RR relative risk, *HR* hazard ratio, *CI* confidence interval, *DFS* disease-free survival, *DSS* disease-specific survival, OS overall survival, *ACE-27* adult comorbidity evaluation-27, *BOT* base of tongue, *ECE* extracapsular extension, *PNI* perineural invasion, *LVI* lymphovascular invasion, *NA* not applicable

nodes, and not ECE or N classification, correlated with a poorer prognosis. On the other hand, Funk et al.[18] concluded that patients with intermediate- or high-risk features should receive adjuvant therapy despite successful salvage for all their patients.

Patients treated with surgery and offered adjuvant therapy based on multidisciplinary recommendations have excellent oncologic outcomes. With relatively low recurrence rates of 9% locally and 14% regionally for patients undergoing surgery alone, our results demonstrate that locoregional recurrence for patients who have undergone surgical therapy alone does not portend a worse prognosis for survival. Patients who are offered or choose close observation after surgery instead of adjuvant therapy have a similar OS despite a higher risk of locoregional recurrence. This may be secondary to the potential availability of all methods for locoregional salvage. On the other hand, this may be limited by sample size, with a larger sample perhaps showing significant differences in survival between the two groups. Therefore, future trials could be designed in which properly selected patients receive surgery alone with close observation, using radiation therapy, chemotherapy, or further surgery for recurrent disease. This could potentially eliminate adjuvant therapy for the majority of this patient population and thus decrease the risk of toxicities from these treatments.

This study had several limitations. First, it was limited by the retrospective nature of the study design and data collection. Second, the low number of recurrence events made it difficult to compare outcomes between groups. It also was limited by the random nature of the matching process. Nearly all the surgery-alone patients were included in the analysis, but only 105 of 306 patients who received adjuvant therapy were included although such exclusion was essential to ensure a balance of known important confounders. We cannot definitively apply these results to the entire population because many recurrence events were not included secondary to the matching process. Finally, several variables that may have prognostic implications could not be evaluated such as tumor volume, extent of radiation fields, and radiation dose.

CONCLUSIONS

Transoral surgery continues to play a role in the treatment of HPV-related oropharyngeal carcinoma, with a majority of patients avoiding recurrence after surgery alone. Secondary to lower locoregional recurrence,

TABLE 4 Characteristics and outcomes of patients with a recurrence

Patient	Primary site	Treatment	T stage	Node number	LVI	PNI	ECE	Margins	Recurrence site	Salvage	Status	OS (months)	DFS (months)	Follow-up after recurrence (months)
1	Tonsil	S	1	0	–	–	NA	–	Local	S + R	ANED	95	59	36
2	BOT	S	1	5	+	–	+	–	Regional	S	ANED	54	4	50
3	BOT	S	4a	1	–	–	–	–	Local	R + C	ANED	45	10	35
4	BOT	S	1	1	–	–	–	–	Local regional	S	ANED	44	43	1
5	Tonsil	S	3	0	–	–	NA	–	Regional[a]	S	ANED	30	23	7
6	Tonsil	S	1	1	–	–	–	–	Regional	S + R	ANED	25	1	24
7	Tonsil	S	2	8	+	+	+	–	Regional	R	ANED	21	6	15
8	Tonsil	S	2	2	–	–	–	–	Regional[a]	S + R	ANED	59	8	51
9	Tonsil	S	2	0	–	–	NA	–	Regional	S + R + C	ANED	88	9	79
10	BOT	S	2	0	–	–	NA	–	Local	S + R+ C	ANED	89	35	54
11	Tonsil	S	2	0	–	–	NA	–	Local	S + R	ANED	40	3	37
12	BOT	S	1	1	–	–	–	–	Regional	S	ANED	37	23	14
13	Tonsil	S	2	2	–	–	+	–	Regional	S + R + C	ANED	36	4	32
14	Tonsil	S	1	0	–	–	NA	–	Local	R + C	ANED	67	10	57
15	Tonsil	S	2	3	–	+	+	–	Regional	R	AWD	5	5	0
16	Tonsil	S	3	1	–	–	–	–	Local	R + C	AWD	50	50	0
17	BOT	S	4a	3	–	–	+	–	Regional	Unknown	AWD	7	7	0
18	BOT	S	3	3	+	+	+	+	Local	Refused	DOD	29	12	17
19	BOT	S	2	5	–	–	+	–	Local	S	DOD	23	6	17
20	Tonsil	S	1	1	–	–	–	–	Regional	R + C	DOD	11	3	8
21	Tonsil	S	1	1	–	–	+	–	Regional[b]	S + R	DOD	32	9	23
22	Tonsil	S	4a	4	+	+	+	–	Regional distant[a]	S + C	DOD	84	36	48
23	Tonsil	S	2	1	+	–	–	–	Regional distant	S + R	DOD	41	19	22
24	Tonsil	S + R	2	1	–	–	–	–	Local	C	DOD	17	7	10
25	BOT	S + R+C	2	1	–	–	+	–	Local	R + C	ANED	14	6	8
26	BOT	S + R+C	4a	13	+	–	+	–	Distant	C	DOD	31	30	1

LVI lymphovascular invasion, *PNI* perineural invasion, *ECE* extracapsular extension, *OS* overall survival, *DFS* disease-free survival, *S* surgery, *NA* not applicable, *R* radiation, *ANED* alive no evidence of disease; *BOT* base of tongue; *C* chemotherapy, *AWD* alive with disease, *DOD* dead of disease

[a] Regional recurrence was in the contralateral, untreated neck. Patient 22 ultimately died of distant metastatic disease without further recurrence of regional disease after contralateral neck dissection

[b] Patient also had metastatic breast cancer in revision neck dissection specimen, so it is not entirely known whether the patient died of recurrent oropharyngeal carcinoma or metastatic breast cancer

adjuvant therapy is associated with improved DFS, without significant improvement in OS or DSS. As we move forward in the management of HPV-related OPSCCa, we must weigh carefully the morbidity and costs of our treatments and the reasons for adding additional therapy. Trials comparing surgery with adjuvant therapy and surgery alone with close follow-up evaluation would be needed to study the true effects of adjuvant therapy. With relatively low local and regional recurrence rates and fairly successful salvage after surgery alone, adjuvant therapy could potentially be spared for a select subset of patients and reserved for recurrent disease, given the similar OS between the two groups.

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