The Benefit of Adjuvant Radiation in Surgically-Treated T1-2 N1 Oropharyngeal Squamous Cell Carcinoma

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Importance: The benefit of adjuvant radiation in surgically treated T1-2N1 oropharyngeal cancer without adverse pathologic features remains unclear

Objectives: To compare population-level survival outcomes in surgically-treated T1-2N1 oropharyngeal squamous cell carcinoma (OPSCC) with and without the use of adjuvant radiation.

Study Design: Retrospective population-based study using the Surveillance, Epidemiology, and End Results (SEER) registry data from 1998–2011.

Setting: Population-level study.

Participants: Patients with T1-2N1 OPSCC treated with surgical resection and neck dissection with or without adjuvant radiation.

Intervention(s) for Clinical Trials or Exposure(s) for observational studies: The use of postoperative adjuvant radiation.

Main Outcome(s) and Measures: Overall and disease-specific survival.

Results: Radiation was utilized in 74% of patients and was positively associated with extracapsular extension and well-differentiated histology. The use of radiation was associated with improved mean overall survival (124 v. 108 months, p=0.023) and a non-significant increase in mean disease-specific survival (138 v. 131 months, p=0.053).

Conclusions and Relevance: The use of adjuvant radiation is associated with improved survival in surgically-treated T1-2N1 squamous cell carcinoma of the oropharynx with unknown HPV status.

Key Words: Oropharynx, survival, lymph node, N1, tonsil, base of tongue, radiation, surgery, squamous cell carcinoma, TORS, robotic.

Level of Evidence: IV

INTRODUCTION

The age-adjusted incidence rate of oropharyngeal cancer has been rising rapidly. Between 2000 and 2011, the age-adjusted incidence rate of oropharyngeal squamous cell carcinoma (OPSCC) increased from an estimated 1.61 to 2.2 cases per 100,000 person/years.[1] This recent rise has been largely attributed to a rising burden of human papillomavirus (HPV)-associated cancers at the same time a decline has been noted in tobacco-related oropharyngeal cancer.[2]

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Concurrent radiation and chemotherapy has become the most common treatment for advanced-staged OPSCC.[3] This combined therapy is well-known to be associated with significant acute and long-term toxicities, mucositis, radiation fibrosis, early and late dysphagia, aspiration, hypothyroidism, carotid atherosclerosis, and stroke.[4–12] In recognition of this, new therapeutic strategies that attempt to reduce the toxicity of treatment are under investigation.[13,14] Included among these is a reinvigoration of the surgical management of OPSCC through the use of transoral robotic and laser microsurgery techniques.[15,16] The reported goal of these surgical modalities is to reduce long-term treatment toxicity through a reduction in the frequency of chemotherapy and radiation utilization, or if radiation is required, to reduce the overall radiation dose. This theory is currently being evaluated in several prospective trials.[14,17]

Occult spread to regional lymphatics occurs frequently in early stage OPSCC.[18,19] In recognition of this, current National Comprehensive Cancer Network (NCCN) treatment guidelines recommend elective neck dissection for surgically managed oropharyngeal cancer.[20] For patients with a pathologically confirmed single positive node, current treatment recommendations offer either observation or adjuvant radiation as potential treatment options. Little data is available to help guide this decision. The primary objective of this study is to evaluate the impact of adjuvant radiation on overall and

TABLE I.
Population Characteristics

Variable	Mean (SEM)/Frequency (%)
Age (yrs)	56.7 (0.539)
Gender	
Male	313 (76.3%)
Female	97 (23.7%)
Ethnicity	
White	372 (90.7%)
Black	18 (4.4%)
Asian or Pacific Islander	14 (3.4%)
Other	6 (1.5%)
Marital Status	
Divorced/Separated/Widowed	74 (18.0%)
Married	273 (66.6%)
Single (never married)	43 (10.5%)
Unknown	20 (4.9)
Primary Site	
Tonsil & lateral pharyngeal wall	257 (62.7%)
Base of tongue	134 (32.7%)
Soft Palate	14 (3.4%)
Posterior pharyngeal wall	2 (0.5%)
Oropharynx, NOS	3 (0.7%)
T Stage	
T1	201 (49%)
T2	209 (51%)
Grade	
Well differentiated	21 (5.1%)
Moderately differentiated	166 (40.5%)
Poorly & undifferentiated	205 (50%)
Unknown	18 (4.4%)
Adjuvant Radiation	
Yes	303 (73.9%)
No	107 (26.2%)
Overall Survival (mos)	120 (3.89)
Disease Specific Survival (mos)	137 (3.32)

SEM: standard error of the mean; NOS: not otherwise specified.

disease-specific survival in T1-2N1M0 surgically-treated squamous cell carcinoma of the oropharynx using population-level data.

METHODS

Database. Data was extracted from the Surveillance, Epidemiology, and End Results (SEER) public-use data set from 1998 to 2011. During this time period, prospective population-based tumor registries were available in the following 18 areas: the metropolitan areas of San Francisco, Detroit, Los Angeles, Seattle, and Atlanta; the San Jose—Monterey area; Alaska natives; greater and rural Georgia and the states of Connecticut, Hawaii, Iowa, New Mexico, Utah, California, Kentucky, Louisiana, and New Jersey.

Patient Cohort. All patients with T1-2 OPSCC undergoing surgical resection of the primary tumor plus neck dissection were extracted from the SEER database. From this population, cases with a single pathologically confirmed lymph node and no evidence of distant metastatic disease were included in the study (T1-2N1M0). International Classification Disease for Oncology, 3rd Edition (ICD-03) histologic codes 8050/3, 8051/3, 8052/3, 8053/3, 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8077/3, 8078/3, and anatomic subsite codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.2, C10.3, C10.9 were used to identify patients with OPSCC. Patients with a history of other malignant tumors other than nonmelanoma skin cancer and those with incomplete data pertaining to their surgical or radiation treatment were excluded, leaving a total of 410 patients available for analysis. Clinicopathologic data, surgical and radiation treatment details as well as survival outcomes were extracted.

Statistical Analysis. Descriptive statistics were performed using independent t tests and the Mann-Whitney U test for mean comparisons of variables with two groupings. Chi-squared and Fisher's exact test were used to analyze categorical variables. Univariate survival estimates were generated using the Kaplan Meier method and compared with the log-rank test. Statistical analysis was performed using SPSS version 22. All tests were 2-tailed and results were considered significant for p≤0.05.

RESULTS

A total of 410 patients with T1-2N1M0 OPSCC that underwent surgical treatment of the primary and neck were identified. The mean patient age was 56.7 years. Seventy-six percent of the study population was male and 91% was white. The percentage of T1 and T2 lesions was approximately equivalent at 49% and 51%, respectively. The tonsil/lateral pharyngeal wall was the most common subsite (63%), followed by the base of tongue (33%), with the remaining subsites accounting for only a fraction of the total number of cases (Table I). The estimated 5-year overall and disease-specific survival for the study population were 77% and 86%, respectively.

Seventy-four percent of patients received adjuvant radiation. The mean age of those receiving radiation (56 years, SEM 0.571) and those not receiving radiation (58, SEM 1.277) did not differ significantly (p=0.111). Similarly, gender distribution, marital status, ethnicity, tumor location, and T stage distribution did not significantly differ between groups (Table II). Patients receiving radiation were less likely to have well-differentiated tumors (3.0% v. 11.2%, p=0.001) and were more likely to have extracapsular extension (23.6% v. 9.8%, p=0.033).

On univariate analysis of disease-specific survival (DSS), age greater than 70, female gender, African American ethnicity, base-of-tongue location and well-differentiated tumors were associated with reduced disease-specific survival (Table III). The use of radiation was associated with a non-significant improvement in mean DSS (138 v. 131 months, p=0.053; Figure 1).

For overall survival (OS), age greater than 70, female gender, base-of-tongue location and well-differentiated tumors were associated with a reduction in survival. As

TABLE II.
Comparison of Radiation and No Radiation Cohorts

Variable	No Adjuvant Radiation Mean (SEM)/Frequency (%)	Adjuvant Radiation Received Mean (SEM)/Frequency (%)	P value
Age (yrs)	58.11 (1.277)	56.16 (0.571)	0.111
Gender			
Male	76 (71.0%)	237 (78.2%)	0.132
Female	31 (29.0%)	66 (21.8%)	
Ethnicity			
White	99 (92.5%)	273 (90.1%)	0.457
Black	5 (4.7%)	13 (4.3%)	0.868
Asian or Pacific Islander	3 (2.8%)	11 (3.6%)	0.686
Other	0 (0%)	6 (2%)	0.302
Marital status			
Married	63 (64.9%)	210 (71.7%)	0.21
Not married	34 (35.1%)	83 (28.3%)	
Primary site			
Tonsil & lateral pharyngeal wall	62 (57.9%)	195 (64.4%)	0.247
Base of tongue	39 (36.4%)	95 (31.4%)	0.340
Soft palate	4 (3.7%)	10 (3.3%)	0.765
Posterior pharyngeal wall	0 (0%)	2 (0.7%)	1.000
Oropharynx, NOS	2 (1.9%)	1 (0.3%)	0.168
T stage			
T1	54 (50.5%)	147 (48.5%)	0.728
T2	53 (49.5%)	156 (51.5%)	
Grade			
Well differentiated	12 (11.2%)	9 (3.0%)	**0.001**
Moderately differentiated	42 (39.3%)	124 (40.9%)	0.762
Poorly & undifferentiated	47 (43.9%)	150 (49.5%)	0.431
Unknown	3 (2.8%)	15 (5.0%)	0.351
Extracapsular extension*			
Yes	5 (9.8%)	35 (23.6%)	**0.033**
No	46 (90.2%)	113 (76.4%)	
Overall survival (mos)	108.4 (7.845)	123.5 (4.252)	**0.023**
Disease specific survival (mos)	130.8 (6.586)	138.5 (3.740)	0.053

*Less than 50% of the cohort had data pertaining to ECE available, results interpreted with caution.
SEM: standard error of the mean; mos: months; NOS: not otherwise specified.

expected, age $\leq$50 was associated with improved overall survival. The use of adjuvant radiation was associated with a significant improvement in mean OS (124 v. 108 months, p=0.023; Figure 1).

Female patients accounted for 24% of the study population. As previously mentioned, female gender was associated with a significant reduction in both DSS (126 v. 140 mos, p=0.001) and OS (106 v. 140 mos, p=0.01) on univariate analysis (Table III). Female patients presented more often with tumors in the BOT (44% v. 31%, p=0.034) and were less likely to be married (51% v. 76%, p<0.001). No significant difference in the use of radiation therapy was noted between female and male patients (68% v. 76%, p=0.146). Likewise, no significant difference was noted between female and male patients with regards to race, age, tumor grade or histology, T stage, insurance status, or the presence of extracapsular extension.

Well-differentiated tumors were noted in 5% of the total population and were associated with reduced OS when compared to moderately and poorly differentiated tumors. Patients with well-differentiated tumors were less likely to receive adjuvant radiation (43% v. 76%, p=0.003). There were no significant differences noted in patient race, age, T stage, marital status, gender, tumor location, or the presence of extracapsular extension between well-differentiated tumors and those with moderate/poor differentiation.

Tumor location in the base of tongue (BOT) occurred in 33% of the population and was associated with a reduction in both OS (107 v. 130 mos, p<0.001) and DSS (123 v. 145 mos, p<0.001) compared to tumors located within the tonsil and lateral pharyngeal wall. There was a modest increase in patient age noted in those with BOT tumors (57.6 years v. 55.5 years, p=0.036). There was no significant difference in the rates of adjuvant radiation,

TABLE III.
Univariate Survival Analysis

Variable	Mean OS (95% CI)	p	Mean DSS (95% CI)	p
Age (yrs)				
≤50	131 (120–142)	**0.029**	140 (131–150)	0.256
51–69	123 (113–132)	0.227	137 (128–146)	0.858
≥70	75 (10–54)	**<0.001**	107 (86–129)	**0.041**
Gender				
Male	124 (116–132)	**0.01**	140 (133–147)	**0.001**
Female	106 (91–122)		126 (112–140)	
Ethnicity				
White	120 (112–128)	0.561	139 (132–146)	0.102
Black	82 (55–109)	0.206	90 (63–117)	**0.039**
Asian or Pacific Islander	42 (13–71)	0.675	107 (83–131)	0.484
Other	42 (13–71)	0.309	28 (N/A)	0.64
Marital status				
Married	123 (115–132)	0.257	137 (129–145)	0.405
Not married	117 (104–131)		137 (126–148)	
Primary site				
Tonsil & lateral pharyngeal wall	130 (122–138)	**<0.001**	145 (138–152)	**<0.001**
Base of tongue	107 (93–120)		123 (110–136)	
T Stage				
T1	124 (113–134)	0.077	139 (131–147)	0.397
T2	115 (104–125)		134 (124–143)	
Grade				
Well differentiated	83 (55–112)	**0.017**	99 (69–129)	**0.016**
Moderately differentiated	116 (104–127)	0.991	133 (123–143)	0.996
Poorly & undifferentiated	123 (113–134)	0.631	140 (132–148)	0.657
Adjuvant radiation				
Yes	124 (115–132)	**0.023**	138 (131–146)	0.053
No	108 (93–124)		131 (118–144)	

OS: overall survival; DSS: disease specific survival; CI: confidence interval.

race, tumor grace, histology, T stage, marital status or the presence of extracapsular extension.

DISCUSSION

Squamous cell carcinoma of the oropharynx is increasingly becoming a major public health burden, largely due to the increasing incidence of HPV-driven cancers. Between 1998 and 2004, the population-level incidence rate of HPV-associated OPSCC was estimated to increase by 225%, while the rates of non-HPV OPSCC declined by an estimated 50%.[21]

HPV-positive OPSCCs are associated with improved survival compared to those that are HPV negative. In a retrospective analysis of patients in the Radiation Therapy Oncology Group Trial 0129 comparing accelerated-fractionation radiation with cisplatin to standard-fractionation radiation with cisplatin, HPV status was found to a strong and independent risk factor for survival. Three-year overall survival in the HPV-positive cohort averaged 25% points better than the HPV-negative cohort (82.4% v. 57.1%).[22]

In recognition of this improved survival as well as the significant early and late morbidities associated with concurrent chemoradiation for oropharyngeal cancer, a national dialogue has been generated around the topic of therapeutic de-intensification for select populations with OPSCC.[13,14] Transoral surgical resection of the primary tumor and neck dissection with risk-based postoperative adjuvant radiation has been one such proposed strategy for therapeutic de-intensification, with national prospective trials attempting to address this question currently underway.

As experience mounts with surgical treatment of early stage OPSCC, the question of what to do for patients with a single positive lymph node will be encountered with increasing frequency. At present, little evidence is in place to guide this treatment decision. A similar population-based retrospective study utilizing the SEER database evaluated the role of adjuvant radiation in surgically-treated T1-2N1M0 oral cavity cancer and found improved survival in patients receiving adjuvant radiation.[23] However, significant differences in the etiology, response to treatment, and survival between oral cavity and oropharyngeal cancer limit broad extrapolation of these findings. In this study we provide population-level data that demonstrates an association
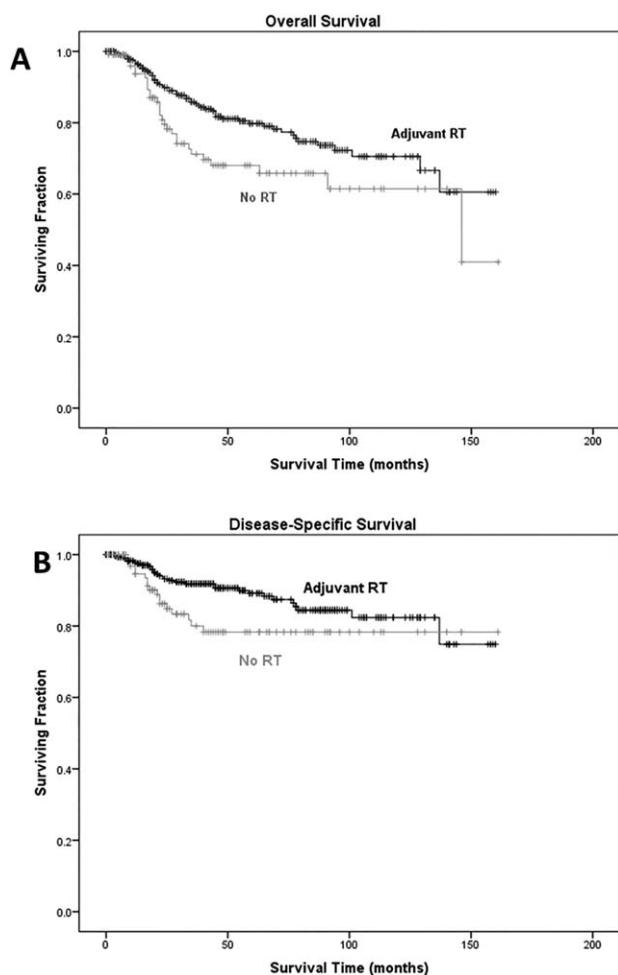
Fig. 1. Kaplan Meier (KM) Survival Curves comparing T1-2N1M0 OPSCC patients treated with surgery with and without adjuvant radiation therapy (RT).
Legend: (A) KM survival curves demonstrating improved OS in patients receiving adjuvant radiation (mean OS 124 v. 108 months, p=0.023). (B) KM survival curves demonstrating non-significant differences in DSS in patients receiving adjuvant radiation with those not (138 v. 131 months, p=0.053).

between the use of radiation therapy and survival outcomes by univariate survival analysis.

Adjuvant radiation was used in 74% of the study population. There were no significant differences in ethnicity, gender, marital status, primary tumor site, or T stage between patients receiving radiation and those not. Importantly, commonly used indications for the use of postoperative adjuvant radiation are not collected by SEER, including the histologic presence of perineural or lymphovascular invasion and the resection margin status. Furthermore, HPV status of the tumors is not available for the study time period. The lack of these prognostic factors does limit the conclusions given our inability to control for known confounding variables. That being said, one can speculate that the use of radiation in this otherwise restricted study population would be based, at least partially, upon the presence of these adverse risk factors. In support of this, the use of adjuvant radiation was positively associated with the presence of extracapsular extension, although this particular variable was only recorded for 49% of the study population, thereby limiting definitive conclusions regarding this relationship.

Interestingly, female gender was associated with lower disease-specific and overall survival in this study population. Female patients in this study group were more likely to have tumors of the base of tongue (44% v. 31%, p=0.034) and were less likely to be married (51% v. 76%, p<0.001), factors that may have influenced the survival outcomes in this group. Female patients were numerically less likely to receive adjuvant radiation (68% v. 76%, p=0.146), although this did not reach statistical significance. It may also be that the disparity in survival between female and male patients reflects the known difference in rates of HPV-positivity between genders, with epidemiologic data demonstrating that HPV-positive tumors are increasing most rapidly in middle-aged white males.[24] It is very likely that the reduction in overall survival noted in patients with well-differentiated tumors also reflects differences in rates of HPV-positivity, with HPV-positive tumors frequently displaying a moderate to poorly differentiated histology.

Tumor location in the base of tongue was associated with a statistically significant reduction in DSS and OS when compared to tumors located in the tonsil. While a modest increase in patient age was noted for patients with base of tongue tumors (57.6 years v. 55.5 years, p=0.036), this is unlikely to account for all of the differences noted. Lower rates of HPV-positivity have been noted in the base of tongue when compared to the tonsil,[25] and this may play a role in the survival differences noted. Another possible contributing factor could be the fact that transoral resection of base of tongue tumors is technically more challenging than for those located in the tonsil. The increased difficulty in exposure and subsequent tumor extirpation may also contribute to a reduction in survival in this surgically-treated cohort. Further work is needed to see if this reduction in survival is independent of treatment modality and HPV status.

As with any study utilizing the SEER database, certain limitations are unavoidable. The most significant of these is certainly the lack of data on known confounding variables, most notably HPV and smoking status. Because of this inability to control for known important covariates, a meaningful multivariate analysis cannot be performed and knowledge on whether radiation use is independently associated with improved survival remains unclear. It also remains possible that the benefit of adjuvant radiation therapy is not equal between HPV-positive and HPV-negative oropharyngeal cancers. This data should, however, raise concerns about the omission of adjuvant radiation therapy for all surgically treated T1-2N1 oropharyngeal cancer patients until additional information is available demonstrating that it is safe to do so.

The SEER database also lacks information regarding the use of chemotherapy in head and neck cancer treatment and it is conceivable that the use of chemotherapy in patients receiving radiation therapy is partially responsible for the differences in survival noted. Additionally, oral cavity and oropharyngeal squamous

cell carcinoma are also known to be under-reported as a cause of death,[26] limiting conclusions that can be reached regarding disease-specific survival outcomes. And finally, inclusion of cases up to 2011 introduces potential selection bias as recent cases only have 2 years of follow-up data available. Given the relatively recent increase in support for surgical treatment of oropharyngeal cancer, inclusion of recent cases was deemed necessary in order to evaluate current practice patterns.

In this study the use of adjuvant radiation was associated with a significant improvement in overall survival for T1-2N1M0 oropharyngeal cancer patients. Further work is needed to understand the benefit of adjuvant radiation in this patient population, particularly as it pertains to other risk factors such as HPV and smoking status. In light of these findings, current attempts to de-escalate therapy in oropharyngeal cancer should be undertaken cautiously in order to avoid compromising survival.

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