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Effect of adjuvant radiotherapy treatment center volume on overall survival*

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Abstract

Objectives: to examine the impact of radiotherapy center volume on overall survival in patients with oral cavity and oropharyngeal squamous cell carcinoma getting adjuvant radiation therapy after receiving surgery at a high-volume center.

Materials and Methods: a retrospective study was conducted on patients with oral cavity squamous cell carcinoma or oropharyngeal squamous cell carcinoma treated surgically at a tertiary institution from 2000 to 2012 who received adjuvant radiotherapy. The outcome variable was overall survival and the independent variable was location of adjuvant radiation therapy: high-volume center (HVC) versus low-volume center (LVC). Cox proportional hazards models were used to assess associations between predictors of death. Variables that were found to be significant at the $\alpha = 0.10$ were included in a multivariable model.

Results: 336 patients met inclusion criteria. One-hundred thirty-nine patients received adjuvant radiation therapy at HVC and 197 patients received adjuvant radiation therapy at LVC. A univariate Cox proportional hazards model identified the variables location, age, marital status,

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Conflict of interest statement

None declared by any of the authors.

subsite, T stage, extracapsular extension, and smoking status to include in a multivariable model. Age, subsite, T stage, and extracapsular extension were independent predictors of overall survival ($p < .05$). Location ($p=.55$), marital status ($p=.29$), and smoking status ($p=.22$) were not statistically significant predictors of survival.

Conclusion: After surgery at a HVC, the volume of adjuvant radiation therapy center was not significantly associated with overall survival. Significant predictors of survival included age, subsite, T stage, and extracapsular extension.

Keywords

Oropharyngeal cancer; Oral cavity cancer; Institution volume; Physician volume; Radiation therapy; Adjuvant therapy; Healthcare outcomes; Head and neck cancer; Overall survival

Introduction

The association between healthcare outcomes and institution and physician volume is ubiquitous in the medical literature regardless of case volume definitions and outcomes assessed [1,2]. There is a documented positive association between institution volume and healthcare outcomes as well as physician volume and healthcare outcomes for a wide range of procedures and conditions [3]. It has been postulated that increased experience and practice may account for this association. However, others have argued that improved outcomes, particularly with publicly reported results, may attract a larger volume of patients due to increased referrals [3].

A meta-analysis examining head and neck oncology procedures documented an association between both institution and physician volume and health outcomes such as short-term survival, long-term survival, and length of stay [4]. A population based study able to examine both institution and surgeon volume also demonstrated an association with overall survival, with the effect largely being mediated at the level of institution volume [5]. The authors suggested that since head and neck cancer procedures require an extended length of stay, intensive care unit admission, and/or multidisciplinary in-patient or out-patient care, the relationship could be largely explained by institution volume, since a large multidisciplinary team and many hospital processes are required to achieve high-quality care [4,5]. Therefore, the National Comprehensive Cancer Network (NCCN), recommends that patients be treated at high-volume centers [6].

Although data on hospital volume and oncological procedures' outcome are established, data on radiation oncology are limited. Recent studies have assessed the association between radiation oncologist volume in the management of nasopharyngeal carcinoma and 5 year and 10 year overall survival [7,8]. A recent landmark study demonstrated higher overall survival in stage III and IV head and neck cancer patients receiving primary radiation or chemoradiation at historically high-accrual into trials centers (HHAC) versus historically low-accrual centers (HLAC) [9]. In these studies, the radiation therapy was the primary treatment modality and the impact of radiation oncology case volume on outcomes in the adjuvant setting is yet unknown.

This study aimed to examine the impact of radiotherapy center treatment experience on overall survival in patients with advanced oral cavity (OCSCC) and oropharyngeal squamous cell carcinoma (OPSCC) receiving adjuvant radiation therapy after primary surgery at a tertiary, National Cancer Institute-designated Cancer Center.

Materials and methods

Study sample and primary predictor

After approval by The Ohio State University Wexner Medical Center (OSUMC) Institutional Review Board, a retrospective study was conducted on patients with primary OCSCC or OPSCC treated surgically at a National Cancer Institute-designated Cancer Center from 2000 to 2012 who received adjuvant radiotherapy. Adjuvant radiation therapy center volume was either at a high-volume center (HVC) at the OSUWMC or low-volume center (LVC) at a variety of local radiation centers. During this time, our institution treated most patients with 3D conformal radiotherapy, with only a minor subset of patients being treated with intensity-modulated radiation therapy (IMRT). Patients were excluded if they were under the age of 18 or if they presented with metastatic disease.

Study variables

The primary outcome, overall survival, was defined as the time from the date of surgery to the date of death, with patients alive at the date of the last observation censored. The main predictor variable was location of adjuvant radiation therapy. Our tertiary institution was defined as HVC and other central Ohio radiation centers were defined as LVC. These centers range from 30 min to 3 h away from the OSUMC and do not have a high volume surgical program or a multidisciplinary tumor board. Other independent variables of interest included age, sex, race (white versus other), marital status (married, divorced, single, widowed), subsite (OPSCC versus OCSCC), tumor (T) stage, nodal (N) stage, and overall stage based on the American Joint Committee on Cancer (AJCC) Stage (7th edition), extracapsular extension, margin status (negative versus positive), adjuvant therapy (radiation versus chemoradiation), smoking status (current, past, or never), and pack years of smoking as continuous variable. Progression-free survival and disease-free survival were not analyzed as many patients received their long-term follow up locally.

Statistical analysis

Descriptive statistics were used to characterize the study population, also stratified by radiation therapy center volume. Comparisons between HVC and LVC patients were assessed via two-sample t-tests or Mann-Whitney tests, depending on distribution of the data for quantitative outcomes and chi-squared or Fisher's exact tests for categorical outcomes. A survival curve was plotted using the Kaplan-Meier method. Cox proportional hazards models were used to assess univariable associations between potential predictors for death. Unadjusted hazard ratios (HR) and 95% confidence intervals (CI) are reported. Variables that were found to be significant at the $\alpha = 0.10$ level in the univariable models were included in a multivariable model to estimate adjusted HRs. Statistical analysis was conducted in SAS version 14.2 (SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

Three-hundred thirty-six patients with primary OCSCC (n = 120) or OPSCC (n = 216) met inclusion criteria (Table 1). The mean age over the entire sample was 58.2 ± 10.4 . Most patients, 251/336 (74.7%), were male. Additionally, 189/320 (59.1%) of patients were married and 304/318 (95.6%) of patients were white. Most patients, 251/329 (76.3%) were current or past smokers with a median of 26 smoke pack years. In terms of staging, 217/336 (64.6%) of patients are staged at T stage 1/2 and 119/336 (35.4%) are at T stage 3/4. Most patients were N stage 2, 191/334 (57.2%), and 53/334 (15.9%) of patients had an N of 0. Finally, 234/334 (70.1%) of patients were categorized by the AJCC to be stage 4, 80/334 (23.9%) patients were at stage 3, and 20/336 (6%) at stages 1/2.

One-hundred thirty-nine (41.4%) patients received adjuvant therapy at HVC and 197 patients (58.6%) received adjuvant therapy at LVC. Patients treated at LVC were older, more likely to be white, to have OCSCC, to have a higher T-stage, to have had radiation versus chemoradiation, and to have more smoking pack years.

Univariable analysis

A univariate Cox proportional hazards model identified the treatment location (HVC vs. LVC) (HR, 0.73; 95% CI, 0.524–1.018; $p = .063$), age (HR, 1.017; 95% CI, 1.002–1.033; $p = .030$), marital status (married versus divorced/single/widowed) (HR, 0.148; 95% CI, 1.064–2.058; $p = .02$), subsite (OCSCC versus OPSCC) (HR, 0.40; 95% CI, 0.288–0.543; $p < .0001$), T stage (T1 versus T4) (HR, 4.826; 95% CI, 2.817–8.268; $p < .0001$), extracapsular extension (HR, 1.49; 95% CI, 1.080–2.062; $p = .015$), smoke pack years (HR, 1.007; 95% CI, 1.002–1.013; $p = .019$), and smoking status (current versus never) (HR, 0.6; 95% CI, 0.392–0.92; $p = .019$), as variables to include in a multivariable model based on an alpha of < 0.10 (Table 2). The overall survival rate for HVC at 1, 3, 5, 10 years was 82.7%, 68.2%, 64.8%, and 58.0%, respectively. The overall survival rate for LVC at 1, 3, 5, 10 years was 84.2%, 63.9%, 56.7%, and 36.5%, respectively. There was no statistically significant difference in survival between LVC and HVC, $p = .063$ (Fig. 1).

Multivariable analysis

Smoke pack years was removed from multivariable model due to collinearity with the variable smoking status. After adjusting for important confounders, age (HR, 1.020; 95% CI, 1.003–1.038; $p = .024$), subsite (OCSCC versus OPSCC) (HR, 0.371; 95% CI, 0.259–0.532; $p < .0001$), T stage (T4 versus T1) (HR, 3.540; 95% CI, 1.975–6.344; $p < .0001$), and extracapsular extension (HR, 1.872; 95% CI, 1.298–2.700; $p = .0008$) were all significant predictors of overall survival. Adjuvant treatment site (HVC vs. LVC) (HR, 1.129; 95% CI, 0.782–1.629; $p = .52$), marital status (married versus divorced/single/widowed) (HR, 1.270; 95% CI, 0.883–1.827; $p = .20$), and smoking status (current versus never) (HR, 0.746; 95% CI, 0.468–1.191; $p = .22$) were not statistically significant predictors of survival (Table 3).

Discussion

Our study demonstrates that radiation center case volume providing adjuvant radiotherapy for patients OCSCC and OPSCC managed with surgery and adjuvant radiotherapy did not predict overall survival on univariable analysis (HR 0.73; 95% CI 0.524–1.018; $p = .063$) and the effect was further attenuated on multivariable analysis (HR, 1.129; 95% CI, 0.782–1.629; $p = .52$). Other important independent predictors of overall survival in our model were age, subsite, T-stage, and extracapsular extension.

Two studies assessed the relationship between radiation oncologist case volume and 5 year and 10 year survival in nasopharyngeal carcinoma where radiation or chemoradiation was used as definitive primary treatment. Chien et al., identified a 13% difference (77% vs 64%) in 5 year survival between high and low radiation oncologist volume ($p = .007$) [7]. Similarly, Lee et al., identified a 14% difference (75% vs 61%) in 10 year survival between high and low radiation oncologist volume ($p < .001$) [8].

Wuthrick et al., assessed the effect of institutional experience on overall survival in patients with stage III or IV head and neck cancer, who received definitive chemoradiation therapy [9]. As a surrogate for experience, institutions were classified as historically low- (HLACs) or high-accruing centers (HHACs) based on accrual to 21 Radiation Therapy Oncology Group head and neck cancer trials. When compared with HHACs, patients at HLACs had worse overall survival on univariable (5 years: 51.0% v 69.1%; $p = .002$) and multivariable analysis (HR, 1.91; 95% CI, 1.37–2.65). These results suggest that patients with head and neck cancer of a more advanced stage, may benefit from treatment at a HHAC. Institutions with higher enrollment into clinical trials, are likely higher volume institutions, with increased infrastructure and resources for multidisciplinary care and adherence to guideline recommended processes of care [10].

Our study has several strengths. To the best of our knowledge, our study is the first to address radiation oncology center volume as it relates to outcomes in the adjuvant setting. We demonstrated that after controlling for important covariates, radiation oncology center volume is not an independent predictor of survival. This is an important consideration because many patients, particularly in our jurisdiction, have a significant travel burden to come to a HVC and would prefer receiving adjuvant treatment locally. This has been studied extensively in Australia where not only have patients complained about a travel-related and caregiver burden, but a significant financial burden as well [11,12]. Because our cohorts' primary outcome had sufficient events, our multivariable analysis controlled for important unbalanced confounders between our primary predictor.

These data must be interpreted in the context of the study design. An important limitation of this study is that most patients during the study were treated with 3D conformal radiotherapy. IMRT, a more skill intensive technique, continues to increase in utilization and may lead to differences in survival in the future [13]. Currently, IMRT is solely being used by our institution. Another limitation is that we focused on population of patients with cancers of the oral cavity and oropharynx, and excluded patients with cancers of the sinonasal and nasopharyngeal subsites where shielding the eye, brain and cranial nerves can

be more challenging without decreasing the effectiveness of the treatment. Furthermore, we included patients of all stages and the impact of radiation center treatment volume may be limited to patients with advanced stage only [9]. We could not perform an analysis of progression free or disease-free survival due to the nature of our referral center. Many patients chose to have their long-term follow up so survival data was the one reliable outcome to provide an analysis. Our study was not able to account for both surgeon and radiation oncologist case volume simultaneously given that all our patients were treated at a very high surgical volume institution. Another limitation of our study is that we used treatment center case volume, a structure measure, as a surrogate marker for quality of care, without having the ability to address adherence to important quality metrics at both high and low volume radiation oncology centers. These metrics include multidisciplinary management with dentistry, speech language pathology, dieticians, and lymphedema therapists. From our experience, access to these important adjunct resources can sometimes have the greatest impact on patients' quality of life and functional outcomes [14]. Additionally, although patients treated at HVC were more likely to have had adjuvant chemoradiation in our cohort, we found no association between adjuvant chemoradiation and worse overall survival. Therefore, chemotherapy is unlikely to have played a role in the similarity in overall survival between both patient populations. Finally, p16 (HPV) status was not recorded in these samples; instead, we used the variable subsite (OCSCC versus OPSCC) as a surrogate to compare tumors that are usually associated with HPV and tumors that are not.

Patients treated at HVC were more likely to have less aggressive OPSCC despite having similar overall survival further supporting that radiation oncology center volume is not an independent predictor of survival. Ultimately, a prospective study with a larger sample size can address limitations of a retrospective study, and can dilute the limited benefit of radiation therapy in the adjuvant setting. Additionally, further studies are needed to address the effect of radiation oncology center volume on subsets of high-risk populations.

Our study has several implications. After surgery at a HVC, adjuvant radiotherapy can be appropriately done at either a LVC or HVC with no significant difference in survival. Adjuvant radiotherapy at a local radiation center can be beneficial to patients. Staying close to home for treatment can save on time, cost of travel and accommodations, and time away from work. Additionally, it has been well established that surgery treatment center experience, particularly oncological in nature, is a predictor of both perioperative outcomes and survival [15,16]. With a multimodality treatment approach to head and neck cancer as in this study, the surgery center experience may be the most important determining factor of overall survival. When patients are consented for surgery and adjuvant therapy is discussed, some patients hesitate to proceed with curative management because of an inability to come to radiotherapy at our center. Despite a lack of multidisciplinary management with adjunct resources at lower volume radiation oncology centers, in cases where patients may refuse treatment altogether, it may be worthwhile to allow patients to receive their adjuvant treatment closer to their primary residence.

Conclusion

After surgery at tertiary, high-volume center, the volume of adjuvant radiation therapy center does not predict overall survival in the pre-IMRT era. Important predictors of survival include age, subsite, T-stage, and extracapsular extension. Future investigation is needed now that IMRT is the standard of care and is more technically challenging. This may result in significant survival difference according to treatment center experience but should be subjected to further analysis.

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Abbreviations:

AJCC	American Joint Committee on Cancer
CI	confidence interval
HHAC	historically high accrual centers
HLAC	historically low-accrual centers
HR	hazard ratio
HVC	high volume center
IMRT	intensity-modulated radiation therapy
LVC	low volume center
OCSCC	oral cavity squamous cell carcinoma
OPSCC	oropharynx squamous cell carcinoma
OSUWMC	Ohio State University Wexner Medical Center

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	<i>Survival Rates</i>			
	1 year (%)	3 year (%)	5 year (%)	10 year (%)
Overall	83.6	65.7	60.0	44.6
HVC	82.7	68.2	64.8	58.0
LVC	84.2	63.9	56.7	36.5

Fig. 1.

Caption: Kaplan–Meier Survival by Radiotherapy Treatment Center. Description: patients receiving radiation therapy at high volume center had similar overall survival to patients receiving radiation therapy at a local center ($p = .06$).

Table 1

Patient characteristics – local vs. academic radiation center.

Characteristics	N (%) or Median (IQR)	HVC (n = 139)	LVC (n = 197)	Total (n = 336)	p-value
Mean age in years (SD)		56.0 (9.9)	59.8 (10.4)	58.2 (10.4)	.0009
Gender					
	Female	37 (26.6)	48 (24.4)	85 (25.3)	.6398
	Male	102 (73.4)	149 (75.6)	251 (74.7)	
Marital Status ^a (n = 320)					
	Married	77 (57.5)	112 (60.2)	189 (59.1)	
	Divorced	23 (17.2)	21 (11.3)	44 (13.7)	.4807
	Single	25 (18.7)	37 (19.9)	62 (19.4)	
	Widowed	9 (6.7)	16 (8.6)	25 (7.8)	
Race (n = 318)					.0102 ^b
	White	125 (91.9)	179 (98.4)	304 (95.6)	
	Other	11 (8.1)	3 (1.6)	14 (4.4)	
Subsite					.0071
	OCSCC	38 (27.3)	82 (41.6)	120 (35.7)	
	OPSCC	101 (72.7)	115 (58.4)	216 (64.3)	
T Stage					.0080
	1	41 (29.5)	35 (17.8)	76 (22.6)	
	2	62 (44.6)	79 (40.1)	141 (42.0)	
	3	14 (10.1)	38 (19.3)	52 (15.5)	
	4	22 (15.8)	45 (22.8)	67 (19.9)	
N Stage ^c (n = 334)					.0891
	0	14 (10.1)	39 (19.9)	53 (15.9)	
	1	37 (26.8)	40 (20.4)	77 (23.1)	
	2	81 (58.7)	110 (56.1)	191 (57.2)	
	3	6 (4.4)	7 (3.6)	13 (3.9)	
AJCC Stage ^d (n = 334)					.4787 ^b
	1	1 (0.7)	4 (2.0)	5 (1.5)	
	2	4 (2.9)	11 (5.6)	15 (4.5)	
	3	36 (26.1)	44 (22.4)	80 (23.9)	
	4	97 (70.3)	137 (69.9)	234 (70.1)	
Extracapsular extension					.5043
	44 (32.3)	70 (35.9)	114 (34.4)		
Margin status					.4766
	Negative	111 (81.0)	163 (84.0)	274 (82.8)	
	Positive	26 (19.0)	31 (16.0)	57 (17.2)	
Adjuvant Therapy					< .0001
	Chemoradiation	90 (60.5)	67 (34.7)	157 (47.4)	

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Characteristics	N (%) or Median (IQR)	HVC (n = 139)	LVC (n = 197)	Total (n = 336)	p-value
Smoke pack years	Radiation	48 (34.8)	126 (65.3)	174 (52.6)	
		20 (0, 44)	30 (7, 50)	26 (1.5, 46.5)	.0260
Smoking status	Never	39 (28.3)	39 (20.4)	78 (23.7)	.2008
(n = 329)	Past	54 (39.1)	76 (39.8)	130 (39.5)	
	Current	45 (32.6)	76 (39.8)	121 (36.8)	
Smoking status (pack years) (n = 326)	10	53 (39.0)	55 (28.9)	108 (33.1)	.0580
	> 10	83 (61.0)	135 (71.1)	218 (66.9)	

Notes: values are reported as frequency and column percentages unless otherwise noted. SD, standard deviation. IQR, interquartile range. HVC, high volume center. LVC, low volume center. OCSCC, oral cavity squamous cell carcinoma. OPSCC, oropharynx squamous cell carcinoma.

^aMarital status was condensed to Married versus Divorced/Single/Widowed for statistical analysis purposes.

^bp-values were from fisher exact test.

^cN Stage was condensed into 0, 1, 2/3 for statistical analysis purposes.

^dAJCC Stage was condensed into 1/2, 3/4 for statistical analysis purposes.

Table 2

Overall survival univariable analysis.

Predictor	Level	HR	95%CI		p-value
Location	LVC	Ref			
	HVC	0.730	0.524	1.018	.0638
Age		1.017	1.002	1.033	.0299
Gender	Female	Ref			
	Male	0.979	0.684	1.401	.9084
Marital status	Married	Ref			
	Divorced/Single/Widowed	1.480	1.064	2.058	.0198
Race	White	Ref			
	Other	1.488	0.753	2.939	.2527
Subsite	OCSCC	Ref			
	OPSCC	0.395	0.288	0.543	< .0001
T stage	T1	Ref			
	T2	1.818	1.065	3.104	.0285
	T3	3.354	1.880	5.982	< .0001
	T4	4.826	2.817	8.268	< .0001
N stage	N0	Ref			
	N1	0.729	0.443	1.199	.2129
	N2/N3	0.920	0.603	1.401	.6965
AJCC stage	I/II	Ref			
	III/IV	0.905	0.488	1.677	.7503
Extracapsular extension		1.491	1.080	2.062	.0154
Margin status	Negative	Ref			
	Positive	1.154	0.761	1.751	.4998
Adjuvant therapy	Radiation	Ref			
	Chemoradiation	0.808	0.582	1.122	.2024
Smoke pack years		1.007	1.002	1.013	.0114
Smoking status (history)	Current	Ref			
	Never	0.600	0.392	0.920	.0191
	Past	0.606	0.421	0.871	.0068

Abbreviations: LVC, low volume center. HVC, high volume center. OPSCC, oropharyngeal squamous cell carcinoma. OCSCC, oral cavity squamous cell carcinoma.

Table 3Overall survival multivariable analysis^a.

Predictor	Level	HR	95%CI		p-value
Location	LVC	Ref			
	HVC	1.129	0.782	1.629	.5181
Age		1.020	1.003	1.038	.0237
Marital status	Married	Ref			
	Divorced/Single/Widowed	1.270	0.883	1.827	.1982
Subsite	OCSCC	Ref			
	OPSCC	0.371	0.259	0.532	< .0001
T stage	T1	Ref			
	T2	1.612	0.926	2.806	.0913
	T3	3.245	1.767	5.959	.0001
	T4	3.540	1.975	6.344	< .0001
Extracapsular extension		1.872	1.298	2.700	.0008
Smoking status (history)	Current	Ref			
	Never	0.746	0.468	1.191	.2196
	Past	0.734	0.492	1.095	.1297

Abbreviations: LVC, low volume center. HVC, high volume center. OPSCC, oropharyngeal squamous cell carcinoma. OCSCC, oral cavity squamous cell carcinoma.

^aVariables were entered into the multivariate model if they had a p value of < 0.1 on the univariate analysis.