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Research Article

Impact of Treatment Time on Outcome for Resected Head and Neck Squamous Cell Carcinoma by HPV Status

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ABSTRACT

Background and Purpose: Prior investigations have demonstrated an inverse correlation between the interval from resection of head and neck squamous cell carcinoma (HNSCC) to radiotherapy (RT) completion (overall treatment time; OTT) and disease control. However, the importance of OTT in human papillomavirus (HPV)-associated HNSCC remains to be determined. This study evaluates whether OTT remains independently associated with cancer control when evaluated by HPV association.

Material and Methods: The data of HNSCC patients treated with curative-intent surgical resection followed by RT were collected. Univariable and multivariable analyses were used to assess the effects of HPV association and OTT.

Results: From 2002-2014, 73 eligible patients were identified (36 HPV-associated). The median OTT was 94 days (range, 69-185, with no difference between HPV subgroups). At a median follow-up of 34.9 months (range, 2.6-162.2), 21 patients experienced disease failure, and 25 died. HPV-association was linked to improved disease-free survival (DFS), disease-specific survival (DFS), and overall survival (OS) by univariable and multivariable analyses. OTT was associated with improved DFS by univariable and multivariable analyses.

Conclusion: OTT remains significantly associated with cancer control in the setting of HPV-associated disease. Efforts should be made to minimize the delay between resection and completion of RT for all HNSCC patients.

Introduction

Loco-regionally advanced head and neck squamous cell carcinomas (HNSCC) are commonly managed by surgical resection followed by radiotherapy (RT). A prolonged interval from surgery to the initiation of RT during the treatment of HNSCC has been associated with worse outcomes in several series published before the turn of the century [1-3]. Subsequent studies in the early 2000s found that a prolonged interval from surgical resection to the completion of RT, termed the overall treatment time (OTT), was similarly associated with worse disease control [4, 5].

Over the past two decades, the demographics of HNSCC have shifted. HNSCC had classically been associated with older patients who have significant tobacco exposure [6]. However, there has been a recent rise of human papillomavirus (HPV)-associated HNSCC in younger patients with limited or no history of tobacco use [7, 8]. HPV-associated HNSCC is frequently diagnosed at a loco-regionally advanced stage with a bulky cervical nodal disease [9]. Despite this, its prognosis is superior to tobacco-related, non-HPV-associated disease [10-15].

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While staging and treatment regimens are in the process of being modified to adapt to the changing demographics of HNSCC, HPV-associated tumors are currently managed according to traditional standards-of-care. This standard of care commonly includes surgical resection and radioadjuvant therapy with attention to avoid a prolonged OTT. As the impact of OTT in this context remains undetermined, the present study seeks to determine whether OTT remains independently associated with cancer control in the setting of HPV-associated disease.

Materials and Methods

A single-institution retrospective analysis was performed for patients with non-metastatic HNSCC from the oral cavity or the oropharyngeal primary sites between 2002 and 2014 and treated with curative-intent surgical resection and adjuvant RT (with or without chemotherapy, as indicated). All patients received standard fractionation RT (1.8-2 Gy, once daily, 5 days per week). Patients who received preoperative chemotherapy, did not have tumor HPV data, had incomplete RT records or completion of <90% of the prescribed RT dose or follow-up of less than 12 months post-resection were excluded. Tumor HPV status was determined by p16 immunohistochemistry (IHC), polymerase chain reaction (PCR), or high-risk DNA in situ hybridization (ISH). The use of concurrent chemotherapy was recorded and included in the analysis. Data for each patient was extracted from medical records and verified separately by two investigators.

Chi-square tests, Fisher's exact tests, and Wilcoxon rank sum tests were used to investigate differences between the HPV negative and HPV positive groups. Groups were compared based upon demographics (e.g., age at diagnosis, gender, tobacco use), staging workup (e.g., PET/CT), tumor characteristics (e.g., grade, clinical and pathologic American Joint Committee on Cancer (AJCC) stages, margin status, perineural invasion, lymphovascular invasion, nodal involvement, extracapsular extension), treatment characteristics (e.g., OTT, RT dose, chemotherapy), and follow-up [16]. Overall treatment time was calculated from the date of resection to the end of radiotherapy.

Cox regression models were used to assess the effects of demographic, staging work-up, tumor characteristics, and treatment variables on disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). DFS was calculated from the date of resection to the initial date of clinical or radiographic recurrence, or at last clinical follow-up or death, if no recurrence had occurred. DSS and OS were calculated from the date of resection to the date of death, with events for DSS recorded if death occurred in the context of known recurrence. For patients who died >3 months after their last clinical evaluation (unknown disease status), DFS and DSS were calculated to the date of the last clinical follow-up without recorded event. Due to the limited number of events, only HPV status and OTT were evaluated in the multivariable model. Estimated effects of predictors were calculated as hazard ratios (HR) with 95% confidence intervals.

The Kaplan-Meier method was used to calculate four-year estimates of DFS, DSS, and OS for the entire population, and for HPV and OTT subgroups. Estimates, along with 95% pointwise confidence intervals, were reported. All statistical testing was two-sided and assessed for significance at the 5% level using SAS software (Cary, NC, U.S.A.). This study was approved by the University of Iowa Institutional Review Board.

Table 1: Demographic, clinical, and pathologic characteristics of entire cohort.

	Median (Range)	**n (%) n=73**
Age	59 years (29-82)	
Gender		
Female		20 (27)
HPV Status		
Positive		36 (49)
Primary Site		
Oral Cavity		35 (48)
Oropharynx		38 (52)
Tobacco Use History		
None		21 (29)
≤10 pack-years		12 (17)
>10 pack-years		39 (54)
PET/CT Staging		53 (72)
AJCC Clinical Stage		
1-2		15 (20)
3		23 (31)
4a		35 (48)
Interval, Biopsy to Resection	35 days (0-90)	
TORS approach		22 (30)
Tumor Grade		

1-2 3		43 (59) 30 (41)
Tumor Size	2.1 cm (0.3-6.7)	
Pathologic Nodal Tumor Size (largest)	2.2 cm (0.2-6.5)	
Number LNs Involved	2 (0-32)	
Percent LNs Involved	6% (0-100)	
Extranodal Extension		37 (51)
Perineural Invasion		31 (44)
Lymphovascular Invasion		33 (47)
Final Primary Margin Close (<1 mm) or Positive		31 (42)
AJCC Pathologic Stage 1-3 4		 22 (30) 51 (70)
Concurrent Chemotherapy		26 (36)
Interval, Resection to RT	46.5 days (27-117)	
Interval, RT Start to End	46.5 days (31-111)	
RT Dose	6600 cGy (5000-7200)	
OTT	94 days (69-185)	
Disease Failure		21 (29)
Survival Status Alive Dead		 48 (66) 25 (34)
Length of Follow-up	34.8 months (2-162)	

HPV: human papillomavirus; PET/CT: positron emission tomography/computed tomography; AJCC: American Joint Commission on Cancer; TORS: transoral robotic surgery; LNs: lymph nodes; RT: radiotherapy; OTT: overall treatment time.

Results

Between 2002 and 2014, a total of 98 patients were identified for inclusion, of whom 73 were eligible for the present analysis. Reasons for exclusion were: incomplete RT records (n=10), completion of <90% of RT dose (4), missing tumor HPV data (4), insufficient follow-up (4), receipt of preoperative chemotherapy (2), and metastasis at diagnosis (1). Within the 73 patient study population, 20 (27%) were female, 58 (80%) had AJCC clinical stage III-IV disease, 36 (49%) had HPV-associated tumors, and the median OTT was 94 days (range, 69-185, with no difference between HPV subgroups).

For HPV-associated tumors, the determination was made by p16 IHC in 31 cases, PCR in 1 case, high-risk DNA ISH in 2 cases, and multiple techniques in 2 cases. Detailed patient population characteristics are demonstrated in (Table 1). Differences between the HPV groups are outlined in (Table 2), with HPV-associated tumors more likely to be male, have a limited (or no) tobacco use history, PET/CT staging, oropharynx primary site, higher stage disease at diagnosis, shorter interval from biopsy to surgery, higher-grade tumors, smaller primary tumor size, larger maximal lymph node dimension, and lower rates of perineural invasion (Table 2). Of note, 34 of 38 oropharynx primary cases were HPV-associated, as compared with 2 of 35 oral cavity cases.

At a median follow-up of 34.9 months (range, 2.6-162.2) for all patients and 40.8 months for surviving patients (with 37.5% followed >4 years), 21 patients (28%) experienced disease failure, and 25 (34%) died (17 due to HNSCC). Univariable analysis for the total population demonstrated that higher AJCC clinical stage, oral cavity primary site, tumor grade, larger primary tumor size, and lack of HPV association were linked to worse DFS, DSS, and OS, while longer OTT was associated with lower DFS (Table 3; DSS data not shown). By multivariable analysis, HPV-association and shorter OTT remained significantly associated with improved DFS (Table 4; DSS data not shown). Survival curves with 4-year endpoint estimates for DFS and OS by HPV association and OTT (dichotomized to $\leq$100 versus >100 days) are demonstrated in (Figures 1a/1b & 2a/2b, respectively).

Table 2: Demographic, clinical, and pathologic variables by HPV Status.

	HPV Negative n=37		**HPV Positive n=36**		***p***
	Median (Range)	**n (%)**	**Median (Range)**	**n (%)**	
Age	56 yrs (29-82)		60 yrs (33-76)		0.74
Gender Female		17 (46)		3 (8)	<0.01
Primary Site Oral Cavity Oropharynx		33 (89) 4 (11)		2 (6) 34 (94)	<0.01
Tobacco Use History None ≤10 pack-years >10 pack-years		6 (16) 7 (19) 24 (65)		15 (43) 5 (14) 15 (43)	0.04
PET/CT Staging		22 (60)		31 (86)	0.01
AJCC Clinical Stage 1-2 3 4a		15 (40) 13 (35) 9 (24)		0 (0) 10 (28) 26 (72)	<0.01
Interval, Biopsy to Resection	39 days (7-90)		32 days (0-56)		<0.01
Tumor Grade 1-2 3		31 (84) 6 (16)		12 (33) 24 (67)	<0.01
Tumor Size	3.1 cm (0.9-6.7)		1.8 cm (0.3-4.7)		<0.01
Pathologic Nodal Tumor Size (largest)	1.25 cm (0.2-4.3)		3.5 cm (0.9-6.5)		<0.01
# LNs Involved	2 (0-5)		2 (1-32)		0.57
% LNs Involved	8% (1.6-20)		6% (1.5-56)		0.69
Extranodal Extension		20 (54)		17 (47)	0.56
Perineural Invasion		25 (68)		6 (18)	<0.01
Lymphovascular Invasion		18 (51)		15 (43)	0.47
AJCC Pathologic Stage 1-3 4		11 (30) 26 (70)		11 (31) 35 (69)	0.94
Interval, Resection to RT	45.5 days (27-117)		47.5 days (33-77)		0.55
Interval, RT Start to End	46 days (31-111)		46.5 days (34-60)		0.70
RT Dose	6600 cGy (5000-6996)		6600 cGy (5000-7200)		
Concurrent Chemotherapy		11 (30)		15 (42)	0.29
OTT	94 days (69-185)		93 days (74-120)		0.69

HPV: human papillomavirus; PET/CT: positron emission tomography/computed tomography; AJCC: American Joint Commission on Cancer; LNs: lymph nodes; RT: radiotherapy; OTT: overall treatment time.

Table 3: Univariable analysis of demographic, clinical, and pathologic variables for DFS and OS.

	DFS		**OS**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
Age[a]	0.99 (0.95-1.02)	0.40	1.01 (0.97-1.05)	0.63
Gender				
Female	1.30 (0.52-3.22)	0.57	1.11 (0.47-2.59)	0.81
Primary Site				
Oral Cavity	5.77 (1.93-17.24)	<0.01	4.62 (1.71-12.44)	<0.01
Tobacco Use History				
None	Ref	-	Ref	-
≤10 pack-years	1.05 (0.36-3.07)	0.93	1.61 (0.43-6.02)	0.48
>10 pack-years	2.05 (0.59-7.11)	0.26	1.65 (0.60-4.57)	0.33
PET/CT Staging	1.32 (0.53-3.27)	0.55	1.30 (0.57-3.01)	0.53
Clinical AJCC Stage				
1-2	Ref	-	Ref	-
3	1.32 (0.44-3.92)	0.62	0.88 (0.31-2.49)	0.81
4a	3.89 (1.41-10.76)	<0.01	2.86 (1.13-7.19)	0.03
HPV Negative	7.42 (2.17-25.30)	<0.01	5.43 (1.85-16.00)	<0.01
Interval, Biopsy to Resection[a]	1.02 (0.99-1.04)	0.24	1.02 (1.00-1.04)	0.12
Tumor Grade				
1-2	Ref	0.06	Ref	<0.01
3	2.65 (0.97-7.24)		4.10 (1.40-11.97)	
Tumor Size[a]	1.52 (1.17-1.98)	<0.01	1.29 (1.03-1.63)	0.03
Pathologic Nodal Tumor Size[a] **(largest)**	0.72 (0.47-1.11)	0.14	0.84 (0.59-1.19)	0.33
# LNs Involved[a]	0.95 (0.78-1.16)	0.60	1.03 (0.97-1.10)	0.35
% LNs Involved[a]	0.15 (0.00-32.51)	0.48	1.10 (0.07-18.59)	0.95
Extranodal Extension	1.31 (0.55-3.11)	0.54	1.09 (0.49-2.40)	0.83
Perineural Invasion	2.12 (0.88-5.14)	0.10	1.82 (0.81-4.07)	0.14
Lympovascular Invasion	1.24 (0.51-3.01)	0.63	0.97 (0.43-2.16)	0.93
Final Primary Margin Close (<1 mm) or Positive	1.07 (0.45-2.55)	0.87	2.24 (1.01-4.95)	0.05
AJCC Pathologic Stage				
1-3	Ref	0.58	Ref	0.52
4	1.29 (0.52-3.20)		1.31 (0.57-2.97)	
No Concurrent Chemotherapy	1.19 (0.48-2.95)	0.71	0.95 (0.40-2.24)	0.91
Interval, Resection to RT[a]	1.03 (1.01-1.05)	0.01	1.00 (0.97-1.04)	0.90
Interval, RT Start to End[a]	1.03 (1.01-1.06)	0.02	1.01 (0.98-1.03)	0.62
OTT[a]	1.02 (1.01-1.04)	<0.01	1.01 (0.99-1.02)	0.37

DFS = disease-free survival; OS = overall survival; PET/CT = positron emission tomography/computed tomography; AJCC = American Joint Commission on Cancer; HPV = human papillomavirus; LNs = lymph nodes; RT = radiotherapy; OTT = overall treatment time. [a]Denotes integral units (i.e., 1 year for age, 1 day for intervals including OTT, 1cm for tumor and LN size, 1 LN for number of LNs involved, and 1% for percent LNs involved).

Table 4: Multivariable analysis of DFS and OS by HPV status and OTT.

	DFS		**OS**	
	HR (95% CI)	p	HR (95% CI)	p
HPV Negative	6.56 (1.89-22.79)	<0.01	5.35 (1.80-15.85)	<0.01
OTT[a]	1.02 (1.00-1.03)	0.04	1.00 (0.99-1.02)	0.77

[a]Unit = 1 day.

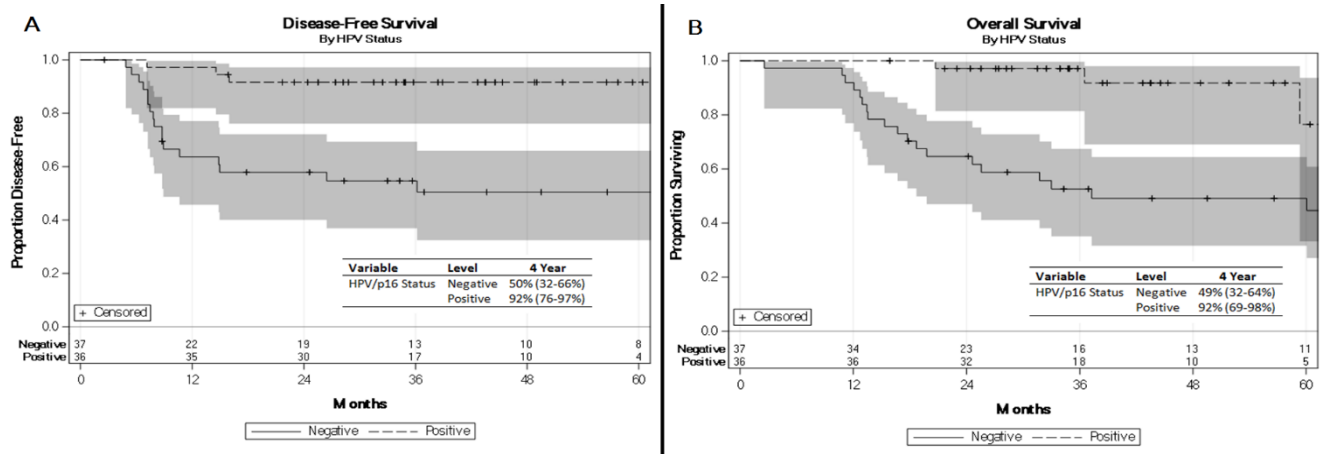

Figure 1: A) Disease-Free Survival by HPV status. **B)** Overall Survival by HPV status.

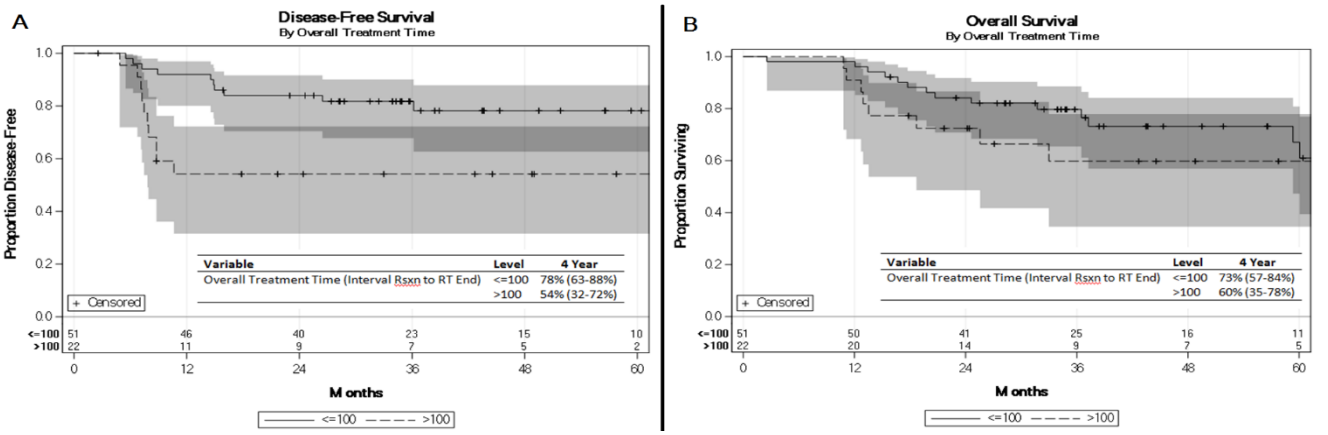

Figure 2: A) Disease-Free Survival by OTT. **B)** Overall Survival by OTT.

Discussion

Prior studies evaluating the impact of the interval from surgery to adjuvant radiotherapy on disease control and survival for HNSCC were performed prior to the reported rise of HPV-associated disease [1-5]. To our knowledge, the present study represents the first analysis of the impact of OTT in the context of HPV-associated disease. The demographic characteristics, primary site distribution, and treatment outcomes for HPV-associated disease within the study population are consistent with previously published reports [7-9]. Hence, the present study population is representative of surgically-managed HNSCC involving oropharyngeal and oral cavity subsites in the population at large.

It is noteworthy, albeit unsurprising that HPV association remained the most critical factor associated with DFS, DSS, and OS endpoints; however, OTT remained significantly associated with DFS in the multivariable analysis. While the OTT interval of 100 days was selected for illustrative purposes and has been employed in a previous OTT study, this should not be seen as a specific threshold [4]. Rather, the data demonstrate a gradient rather than a threshold effect, with the present study suggesting a 2% increase in risk of recurrence for each day of OTT prolongation.

OTT prolongation may be attributable to a longer interval from resection to RT initiation or a prolonged course of RT (initiation to completion). The previous series of definitive RT for HNSCC have demonstrated the adverse impact of the latter on disease control and survival [1, 17-20]. Further, the reduction of the adjuvant RT interval via accelerated fractionation has demonstrated a modest improvement in outcomes [21]. Specific to our own series, increases in either time from resection to RT initiation or from RT initiation to completion were associated with diminished cancer control. As contemporary head and neck radiotherapy treatment planning may require 7-10 days from simulation to treatment initiation, we recommend preoperative consultation with radiation and medical oncologists, as well as early postoperative multidisciplinary evaluation, in order to expedite care and optimize outcomes.

While OTT remained significantly associated with DFS, independent of HPV-association, the magnitude of impact specific to HPV positive or negative subgroups remains to be determined. Preliminary data suggest that HPV-associated tumors are particularly radiosensitive, with several ongoing investigations seeking methods to de-intensify treatment in this subpopulation (e.g., dose reduction) [9]. Larger subsets will be required to report on relative differences in the impact of OTT on HPV positive or negative subgroups.

The rise of HPV-associated HNSCC has been most pronounced in patients with limited tobacco or alcohol exposure, particularly males [7, 8]. These tumors have a high predilection for the oropharynx but are also noted in the oral cavity and other upper aerodigestive tract subsites [7]. We elected to focus on the oral cavity and oropharyngeal sites in our

study for several reasons. First, surgery remains a primary intervention for both of these subsites. Second, the study populations from prior investigations of OTT were primarily composed of oropharyngeal and oral cavity subsites [4, 21]. Third, within our intra-institutional database, pathologic immunohistochemistry- (p16) or DNA-based HPV data was only available for oropharyngeal and oral cavity subsites during the study period.

Conclusion

The present study supports previous findings that HPV-associated HNSCC is associated with improved DFS, DSS, and OS. Further, the findings suggest that OTT remains significantly associated with DFS in the setting of HPV-associated disease. While these data require validation in a larger series, efforts should be made to optimize the interval from resection to adjuvant RT completion.

Funding

None.

Conflicts of Interest

None.

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