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Scientific Article

Association Between Time From Surgery to Radiation Therapy and Multimodality Treatment Outcomes in HPV+ Head and Neck Cancer: A Multi-Institutional Cohort Experience

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Purpose: Oropharyngeal squamous cell cancers (OPSCCs) are traditionally managed with surgery and, if indicated, adjuvant radiation therapy (RT) with or without chemotherapy. NCCN recommends keeping the time from surgery to the start of RT (TSRT) within 6 weeks to avoid possibly compromising patient outcomes. HPV+ OPSCCs behave more favorably than HPV- OPSCCs. We hypothesized that TSRT beyond 6 weeks may not portend poorer outcomes for the former.

Methods: We identified nonmetastatic, high-risk HPV+ OPSCCs treated with multimodal therapy at 2 institutions. Prolonged TSRT was defined as >6 weeks and was evaluated for association with recurrence-free survival (RFS). Radiation treatment time (RTT; time from the first to the last day of RT), total treatment package time (TTPT; time from surgery to the end of adjuvant treatments), de-escalated RT (dose ≤56 Gy), concurrent chemotherapy, smoking history, and treatment institution were evaluated as possible confounders.

Results: In total, 96 patients were included. The median follow-up time was 62 months (4-123 months); 69 patients underwent transoral robotic surgeries, and 27 received open surgeries. The median postoperative RT dose was 60 Gy (50-70.8 Gy). The median TSRT, RTT, and TTPT were 38 days (11-208), 43 days (26-56 days), and 81 days (40-255 days), respectively. Ten patients failed treatment at a median of 8 months (4-64 months). Two locoregional and 4 distant failures occurred in the group without prolonged TSRT, whereas 2 locoregional and 2 distant failures were recorded in the prolonged TSRT group. Prolonged TTPT, de-escalated RT, chemotherapy, smoking history, and treatment institution were not associated with treatment failure. RTT was dropped from our analyses as no events appeared in the prolonged RTT group, and no reliable hazard ratio could be computed.

Conclusions: TSRT > 6 weeks was not significantly associated with inferior outcomes in the postoperative management of HPV+ OPSCCs. Longer TSRT may facilitate better recovery from surgical toxicity, as needed, without compromising oncologic outcomes. The TSRT goal for these cancers should be investigated in future studies.

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Introduction

Oropharyngeal squamous cell carcinomas (OPSCCs) are the most common head and neck (H&N) cancers in the United States. Around 58,000 people will be diagnosed with oropharyngeal cancers, with ~12,000 deaths in 2024.[1] The incidence of these cancers is increasing with time, mostly due to a rise in human papilloma virus (HPV) infections and a consequent increase in HPV+ cancers.[2] HPV- tumors, on the other hand, are declining due to a decrease in the incidence of smoking.[2] HPV+ squamous cell cancers of the head and neck have a better prognosis[3] than HPV- cancers, with improved locoregional control (LRC) and overall survival (OS).[4]

OPSCCs often require multidisciplinary care (MDC), including surgical resection, radiation therapy (RT), and/or chemotherapy, depending on clinical and pathologic risk factors.[5] This necessitates complex coordination between surgical, medical, and radiation oncology. A balance is needed between the completion of treatments in a timely fashion and adequate postsurgical recovery before adjuvant therapy.[6,7] Some patients may also require antecedent procedures, such as nutrition evaluations, feeding tubes, and dental work,[8] to optimize them for adjuvant RT. These must be achieved without sacrificing clinical outcomes.[9]

The National Comprehensive Cancer Network (NCCN) recommends keeping the time from surgery to the start of RT (TSRT) ≤6 weeks.[5] The definitive impacts of delays beyond this timeframe are unclear. Some studies have shown that delays beyond 6 weeks do not affect OS or progression-free survival (PFS).[10–12] Yet others have shown that delays beyond 6 weeks may negatively influence OS and PFS.[13,14] Regardless, the complex nature of MDC coordination combined with unforeseen treatment delays can often make this TSRT goal difficult to achieve.[10,15,16]

Given the favorable prognosis of HPV+ OPSCCs, recent prospective trials have evaluated treatment de-escalation,[17] such as by reducing radiation doses and target volumes[18,19] without compromising outcomes.[20] These promising results led us to retrospectively investigate whether the recommendation to start RT within 6 weeks of surgery, especially considering conflicting reports on the impact of TSRT delays, is pertinent for HPV+ OPSCCs.

Methods

Data source

We retrospectively queried patient databases from Thomas Jefferson University (TJU), an NCI-designated cancer center, and Christiana Care Health System (CCHS), a community hospital. Appropriate approvals were obtained from each institution's institutional review boards.

Patient selection

We identified patients diagnosed with nonmetastatic, high-risk HPV+ OPSCCs who underwent multimodal therapy consisting of upfront surgery followed by adjuvant RT to a total dose of at least 50 Gy with or without chemotherapy between 2012 and 2019. We collected data on patient demographics, types of surgery received (transoral robotic surgery (TORS) versus open surgery), pathologic features, RT regimen, chemotherapy, if received, and treatment institution.

Study variables and endpoints

We calculated TSRT for the patients, with prolonged TSRT defined as >6 weeks (42 days) as specified by the NCCN guidelines.[5]

We additionally collected data on treatment facility, sex, age, smoking history, pathologic T stage, clinical/pathologic N stage, de-escalated RT (<56 Gy), omission or inclusion of chemotherapy, radiation treatment time (RTT), and total treatment package time (TTPT) to assess for potential confounders. These variables were selected as they have been linked to worsened outcomes for H&N patients in the existing literature.[21] RTT was defined as the number of days between the first and the last fraction of RT. RTT >49 days constituted prolonged RTT, which has been linked in a few studies to worse OS.[22] TTPT was defined as the number of days between the surgery and the last day of RT. TTPT >100 days represented a prolonged TTPT and may be linked to worse outcomes.[23] We excluded more granular high-risk features, such as extranodal extension, from our analysis as this information was not available for every patient.

Our endpoint was recurrence-free survival (RFS), defined as the time in months between the end of treatment and disease recurrence at the site of the primary tumor, regional lymph nodes, or the development of metastatic disease.

Statistical analysis

Patient demographics, clinical characteristics, clinical/pathologic staging, treatment details, treatment failures,

and different measures of treatment efficacy were compared between the 2 TSRT groups using 2-sample t tests or Wilcoxon rank sum tests for continuous variables and χ^2 tests or Fisher's exact tests for categorical variables, as appropriate, with statistical significance defined at the alpha level of 0.05.

RFS was summarized by prolonged TSRT (TSRT ≤6 weeks vs TSRT >6 weeks) using the Kaplan-Meier method. To estimate the individual impact of treatment facility, sex, age, smoking history, pathologic T stage, clinical/pathologic N stage, de-escalated RT, chemotherapy, TSRT, and TTPT, and bivariate Cox proportional hazards (PH) regression models were generated. Variables significant at the .10 level were included in a backward selection multivariable Cox PH model. This approach removed variables until those remaining in the final model were significant at the .05 level. Lastly, a full multivariable Cox PH model was generated to include treatment facility, sex, age, smoking history, pathologic T stage, clinical/pathologic N stage, de-escalated RT, chemotherapy, TSRT, and TTPT in a single model. RTT was excluded from all models, as there were no treatment failures for patients reporting more than 49 days of RTT.

Analyses were performed using R statistical software version 4.2.2 (R Core Team, 2022) with Ime4[24] and ImerTest packages[25], Microsoft Excel version 16.63.1 for Mac (Microsoft Corporation), and SAS V9.4 (SAS Institute).

Results

Baseline characteristics

Patient demographics, clinical characteristics, pathologic data, treatment details, treatment failures, and different measures of treatment efficacy are summarized in Tables 1, 2, and 3.

As shown in Table 1, we selected 96 patients from the 2 institutions, with TJU and CCHS contributing 62 (64.6%) and 34 (35.4%); 86 (89.6%) were male, and 10 (10.4%) were female. The median age was 67 years (range, 48-84); 90 (93.8%) of our patients were White, and 6 (6.3%) were African American (AA). The breakdown of current, former, and never smokers was 16 (16.7%), 49 (51.0%), and 31 (32.3%) in the entire cohort. The most common oropharyngeal subsite was the tonsil, constituting 64 (66.7%) primaries, followed by 28 (29.2%) base of tongue primaries. Three (3.1%) patients had a primary tumor of overlapping sites, which signifies involvement of both the tonsil and the base of the tongue, and 1 (1.0%) patient had a primary of an unspecified part of the tongue. Pathologic T stages, per the American Joint Committee on Cancer (AJCC) 8th edition, were 3 (3.1%) T0, 41 (42.7%) T1, 43 (44.8%) T2, and 9 (9.4%) T3. No T4 tumors were represented in our cohort. Pathologic lymph node stages were 7 (7.3%) N0, 67 (69.8%) N1, and 16 (16.7%) N2. 6 (6.3%) of the patients had clinical N stage only.

Table 2 summarizes the treatment details for our patients. A total of 69 (71.9%) patients underwent TORS, whereas 27 (28.1%) underwent open surgeries. Of the patients who had lymph node dissection, the median number of dissected nodes was 34 (range, 0-86), whereas the median number of positive nodes was 2 (range, 0-17), which translates to a median positive lymph node percentage of 7.1% (range, 0-66.7%). Of the patients who had pathologic data on high-risk features, positive margins, ENE, lymphovascular invasion, and perineural invasion were present in 16 (18.2%), 40 (46.5%), 45 (57.7%), and 19 (22.9%), respectively. The median postoperative RT dose was 60 Gy (range, 50-70.8 Gy). More granularly, all 96 patients received an initial dose of 60 Gy (range, 46-63 Gy) in 2 Gy per fraction (range, 2-2.1). A subsequent boost of 6 Gy (range, 6-20 Gy) in 2 Gy per fraction (range, 1.8-2.1 Gy) was given to 47 patients. De-escalated RT (<56 Gy) was given to 21 (21.9%) patients, whereas 75 (78.1%) received ≥56 Gy; 64 (67%) received chemotherapy, and 32 (33%) did not.

As shown in Table 3, the median TSRT was 38 days (range, 11-208 days), the median RTT was 43 days (range, 26-56 days), and the median TTPT was 81 days (range, 40-255 days).

Baseline characteristics were well balanced between patient cohorts dichotomized by TSRT ≤6 weeks and TSRT >6 weeks, with a few statistically significant exceptions. The prolonged TSRT group contained fewer current and former smokers, 12.9% and 35.5%, respectively, and more never-smokers (51.6%). The TSRT ≤6 weeks group contained more current and former smokers, 18.5% and 58.5%, respectively, and fewer never-smokers (23.1%). Another exception was TTPT, with the TSRT ≤6 weeks group experiencing a TTPT of 77 days (range, 40-120 days) and the prolonged TSRT group experiencing a TTPT of 94 days (range, 72-255 days).

Treatment failure

As displayed in Table 3, 10 (10%) patients experienced treatment failure at a median of 8 months (4-64 months) after treatment. Locoregional and distant failures were experienced by 4 (40%) and 6 (60%) patients, respectively. The prolonged TSRT cohort experienced 2 (50.0%) locoregional failures (LRF) and 2 (50.0%) distant failures, whereas those without prolonged TSRT experienced 2 (33.3%) LRFs and 4 (66.7%) distant failures. The 2 groups had no significant difference (P>.99).

LRF sites included the tongue (n = 1), maxillary sinus (n = 1), retropharyngeal space (n = 1), and regional lymph nodes (n = 1). Distant failures occurred in the bones (n = 3), lungs (n = 2), and liver (n = 1).

Table 1 Patient demographic and clinical characteristics dichotomized by time from surgery to RT

		Overall	TSRT ≤6 weeks (N = 65)	TSRT >6 weeks (N = 31)	*P* value*
Treatment facility	CCHS	34 (35.4%)	21 (32.3%)	13 (41.9%)	.356
	TJU	62 (64.6%)	44 (67.7%)	18 (58.1%)	
Sex	Male	86 (89.6%)	60 (92.3%)	26 (83.9%)	.284
	Female	10 (10.4%)	5 (7.7%)	5 (16.1%)	
Age (years)Race	Median (range)	67 (48-84)	67 (48-84)	67 (49-84)	.597
	White	90 (93.8%)	61 (93.8%)	29 (93.5%)	>.999
	African American	6 (6.2%)	4 (6.2%)	2 (6.5%)	
Smoking history	Never	31 (32.3%)	15 (23.1%)	16 (51.6%)	.020†
	Former	49 (51.0%)	38 (58.5%)	11 (35.5%)	
	Current	16 (16.7%)	12 (18.5%)	4 (12.9%)	
Oropharynx subsite	Base of tongue	28 (29.2%)	20 (30.8%)	8 (25.8%)	.085
	Tonsil	64 (66.7%)	44 (67.7%)	20 (64.5%)	
	Tongue	1 (1.0%)	1 (1.5%)	0	
	Overlapping site	3 (3.1%)	0	3 (9.7%)	
pT stage (AJCC 8th Edition)	pT0	3 (3.1%)	1 (1.5%)	2 (6.5%)	.551
	pT1	41 (42.7%)	27 (41.5%)	14 (45.2%)	
	pT2	43 (44.8%)	31 (47.7%)	12 (38.7%)	
	pT3	9 (9.4%)	6 (9.2%)	3 (9.7%)	
pN stage (AJCC 8th Edition)	pN0	7 (7.3%)	3 (4.6%)	4 (12.9%)	.486
	pN1	67 (69.8%)	46 (70.8%)	21 (67.7%)	
	pN2	16 (16.7%)	12 (18.5%)	4 (12.9%)	
	Clinical N stage only	6 (6.3%)	4 (6.2%)	2 (6.5%)	

Abbreviations: TSRT = time from surgery to radiation therapy; CCHS = Christiana Care Health System; TJU = Thomas Jefferson University.
*P values were calculated based on 2-sample t tests or Wilcoxon rank sum tests for continuous variables, and χ^2 tests or Fisher's exact tests for categorical variables, as appropriate.
†$P < .05$.

Table 2 Patient pathologic data and treatment details dichotomized by time from surgery to RT

			Overall	TSRT ≤6 weeks (N = 65)	TSRT >6 weeks (N = 31)	*P* value*
Surgery		Open	27 (28.1%)	16 (24.6%)	11 (35.5%)	.268
		TORS	69 (71.9%)	49 (75.4%)	20 (64.5%)	
Lymph Nodes	Dissected	Median (range)	34 (0-86)	35 (9-82)	28 (0-86)	.099
	Positive	Median (range)	2 (0-17)	2 (0-17)	2 (0-8)	.622
	% Positive	Median (range)	7.14 (0-66.7)	7.14 (0-48.6)	7.28 (0-66.7)	.954
High-Risk Features	Surgical margins	Negative	72 (81.8%)	50 (84.7%)	22 (75.9%)	.310
		Positive	16 (18.2%)	9 (15.3%)	7 (24.1%)	
	Extranodal Extension	Absent	46 (53.5%)	28 (49.1%)	18 (62.1%)	.255
		Present	40 (46.5%)	29 (50.9%)	11 (37.9%)	
	Lymphovascular invasion	No	33 (42.3%)	23 (44.2%)	10 (38.5%)	.627
		Yes	45 (57.7%)	29 (55.8%)	16 (61.5%)	
	Perineural invasion	No	64 (77.1%)	43 (76.8%)	21 (77.8%)	.920
		Yes	19 (22.9%)	13 (23.2%)	6 (22.2%)	
Radiation therapy	Initial dose	Median (range)	60 (46-63)	60 (48-63)	60 (46-60)	.398
	Initial dose per fraction	Median (range)	2 (2-2.1)	2 (2-2.1)	2 (2)	.501
	Boost dose	Median (range)	6.00 (6-20)	6 (6-20)	6.00 (6-10)	.379
	Boost dose per fraction	Median (range)	2 (1.8-2.1)	2 (1.8-2.1)	2 (2)	>.999
	Total dose	Median (range)	60 (50-70.8)	60 (50-70.8)	60 (50-70)	.556
	De-escalated radiation therapy	TD <56 Gy	21 (21.9%)	14 (21.5%)	7 (22.6%)	.908
		TD ≥56 Gy	75 (78.1%)	51 (78.5%)	24 (77.4%)	
Chemotherapy		No	32 (33.3%)	21 (32.3%)	11 (35.5%)	.758
		Yes	64 (66.7%)	44 (67.7%)	20 (64.5%)	

Abbreviations: TSRT = time from surgery to radiation therapy; TD = total dose.
*P values were calculated based on 2-sample t tests or Wilcoxon rank sum tests for continuous variables, and χ^2 tests or Fisher's exact tests for categorical variables, as appropriate.
†$P < .05$.

Table 3 Treatment failure and different measures of treatment efficacy dichotomized by time from surgery to RT

		Overall	TSRT ≤6 weeks (N = 65)	TSRT >6 weeks (N = 31)	*P* value*
Treatment failure	Local	4 (40.0%)	2 (33.3%)	2 (50.0%)	>.999
	Distant	6 (60.0%)	4 (66.7%)	2 (50.0%)	
TSRT days	Median (range)	38 (11-208)	34 (11-42)	49 (43-208)	NA
RTT days	Median (range)	43 (26-56)	43 (26-51)	44 (26-56)	.783
TTPT days	Median (range)	81 (40-255)	77 (40-120)	94 (72-255)	<.001†
Follow-up months	Median (range)	62 (4-123)	63 (4-118)	61 (5-123)	.517

Abbreviations: TSRT = time from surgery to radiation therapy; RTT = radiation treatment time; TTPT = total treatment package time.
**P* values were calculated based on 2-sample *t* tests or Wilcoxon rank sum tests for continuous variables, and χ^2 tests or Fisher's exact tests for categorical variables, as appropriate.
†$P < .05$.

Figure 1 shows the Kaplan-Meier curve for RFS rate dichotomized by TSRT ≤6 weeks versus TSRT >6 weeks. Prolonged TSRT was not associated with a significantly increased risk of failure ($P = .57$).

Bivariate and multivariable analysis for predictors of treatment failure

Bivariate Cox PH regression models were used to examine the individual impact of each predictor on treatment failure and are summarized in Table 4. Except for the clinical/pathologic N stage (clinical N stage only: HR, 0.61 [95% CI, 0.06-6.80]; N1: HR, 0.12 [95% CI, 0.02-0.74]; N2: HR, 0.79 [95% CI, 0.14-4.30]; $P = .056$), no other statistically significant predictors were observed for treatment failure at the $P < .10$ level. The clinical/pathologic N stage was considered for inclusion into a backward selection model, but it resulted in a null model given that this variable was not significant at the $P < .05$ level. A full multivariable Cox PH regression model with all predictors of interest was then performed and is summarized in Table 5. No predictors were statistically significantly associated with treatment failure at $P < .05$.

Discussion

HPV+ OPSCCs have been identified as distinct clinical entities compared with their HPV- counterparts, with their unique biology and improved prognosis.[26] A growing body of evidence has reported treatment de-escalation

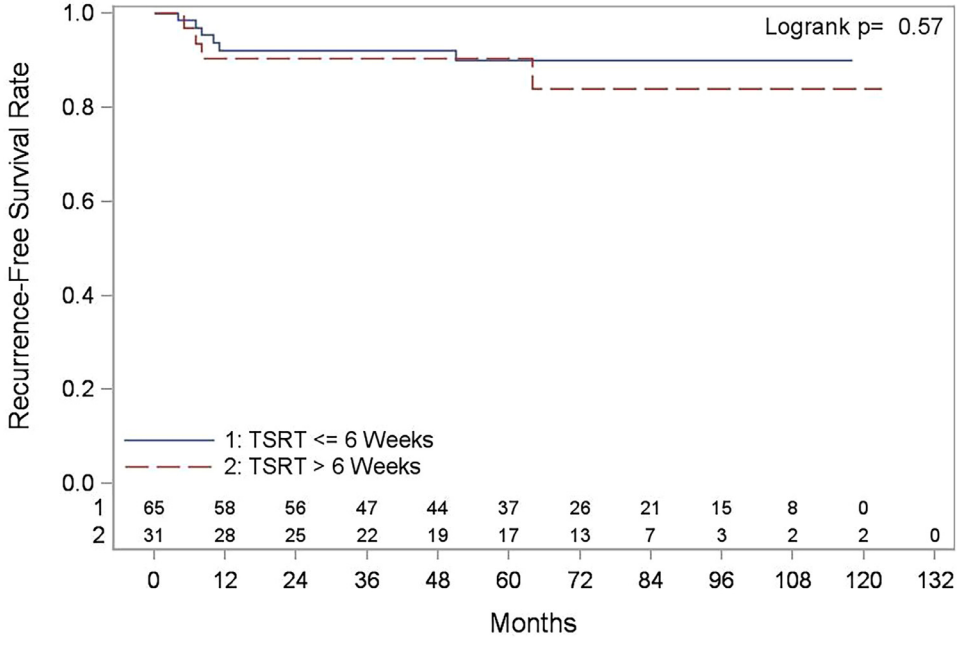

Figure 1 Kaplan-Meier curves and life tables for recurrence-free survival rate by prolonged time from surgery to RT.
Abbreviation: TSRT = time from surgery to radiotherapy.

Table 4 Bivariate Cox regression models for recurrence-free survival

Predictor	Comparison level	Hazard ratio (95% CI)	*P* value
Treatment facility	TJU vs CCHS (REF)	0.69 (0.19, 2.50)	.577
Sex	Male vs Female (REF)	1.00 (0.13, 7.89)	.998
Age (years)		1.04 (0.97, 1.11)	.332
Smoking history	Former or Current vs Never Smoker (REF)	0.71 (0.20, 2.50)	.590
pT stage (AJCC 8th Edition)	T0 vs T1 (REF)	0.00 (0.00,.)	.521
	T2 vs. T1 (REF)	3.31 (0.69, 15.96)	
	T3 vs. T1 (REF)	2.15 (0.19, 23.80)	
pN stage (AJCC 8th Edition)	Clinical N stage only vs N0 (REF)	0.61 (0.06, 6.80)	.056[†]
	N1 vs N0 (REF)	0.12 (0.02, 0.74)	
	N2 vs N0 (REF)	0.79 (0.14, 4.30)	
De-escalated radiation therapy	Total dose <56 Gy vs ≥56 Gy (REF)	0.42 (0.05, 3.35)	.415
Chemotherapy	Yes vs No (REF)	0.75 (0.21, 2.65)	.652
TSRT	TSRT ≤6 weeks vs TSRT >6 weeks (REF)	0.70 (0.20, 2.47)	.576
TTPT	≤100 days vs >100 days (REF)	0.97 (0.12, 7.65)	.975

Abbreviations: REF = reference; TSRT = time from surgery to radiation therapy; TTPT = total treatment package time; CCHS, Christiana Care Health System; TJU, Thomas Jefferson University.
Radiation treatment time was dropped from the bivariate Cox regression model because no events appeared in >49 days, and no reliable hazard ratio could be computed.
†$P < .1$.

Table 5 Multivariable Cox regression models for recurrence-free survival

Predictor	Comparison level	Hazard ratio (95% CI)	P value
Treatment facility	TJU vs CCHS (REF)	0.38 (0.05, 2.78)	.343
Sex	Male vs Female (REF)	2.07 (0.12, 34.39)	.611
Age (years)		1.01 (0.93, 1.09)	.851
Smoking history	Former or Current vs Never Smoker (REF)	0.95 (0.20, 4.37)	.944
pT stage (AJCC 8th Edition)	T0 vs T1 (REF)	0.00 (0.00,.)	.566
	T2 vs T1 (REF)	3.95 (0.60, 26.14)	
	T3 vs T1 (REF)	2.29 (0.15, 35.62)	
pN Stage (AJCC 8th Edition)	Clinical N stage only vs N0 (REF)	0.88 (0.03, 26.30)	.110
	N1 vs N0 (REF)	0.17 (0.01, 2.37)	
	N2 vs N0 (REF)	1.04 (0.06, 17.64)	
De-escalated radiation therapy	Total dose <56 Gy vs ≥56 Gy (REF)	0.19 (0.01, 2.69)	.218
Chemotherapy	Yes vs No (REF)	0.59 (0.11, 3.27)	.543
TSRT	TSRT ≤6 weeks vs TSRT > 6 weeks (REF)	0.59 (0.11, 3.03)	.525
TTPT	≤100 days vs >100 days (REF)	1.48 (0.06, 38.85)	.816

Abbreviations: REF = reference; TSRT = time from surgery to radiation therapy; TTPT = Total Treatment Package Time; CCHS = Christiana Care Health System; TJU = Thomas Jefferson University.
Radiation treatment time was dropped from the multivariate Cox regression model because no events appeared in >49 days, and no reliable hazard ratio could be computed.

for these cancers with favorable outcomes.[17] Our analysis indicates that prolonged TSRT (>6 weeks) may not increase the rate of treatment failures in HPV+ tumors. Allowing for more TSRT may thus be another way to de-intensify treatment while preserving excellent oncologic outcomes.

Head and neck oncologists must often balance competing priorities, including navigating interdisciplinary coordination, allowing adequate healing between surgery and adjuvant treatments and minimizing delays. If TSRT is not as crucial in HPV+ patients, this population may benefit from more extended recovery periods after surgery, as this period poses the greatest risks for surgical morbidity and mortality.[27] A recent treatment de-escalation study randomized HPV+ OPSCCs patients to receive either primary transoral surgery (TOS) followed by dose-reduced adjuvant RT if indicated based on surgical pathology or primary RT with or without weekly chemotherapy (based on lymph node features). The investigators reported 3 deaths, 2 resulting directly from treatment-related toxicities (grade 5 bone infection and oral hemorrhage), in patients randomized to the primary TOS arm. No such deaths or toxicities were noted in the primary RT arm.[28]

NCCN recommends keeping TSRT ≤6 weeks.[5] A literature survey reveals that the benefits of doing so lack consensus. A retrospective study of 41,291 patients from the National Cancer Database revealed that deviation from the NCCN-recommended TSRT is associated with decreased survival.[12] Conversely, a single-institution cohort study of 168 patients showed that TSRT, dichotomized by TSRT ≤92 days versus TSRT >92 days, does not affect LRC.[29] This is noteworthy because the threshold for delayed TSRT was significantly longer than the NCCN recommendations (42 days (6 weeks) versus 92 days (∼13 weeks)). Another study of 111 patients used the guideline-adherent 6-week cutoff for its analysis but echoed the finding that prolonged TSRT alone does not negatively impact LRC.[30] Our finding is more in line with the latter 2 studies. The heterogeneity of the literature on TSRT may indicate that the wide variety of H&N cancers, especially the more favorable HPV+ OPSCCs, need not be held to the standard of TSRT ≤6 weeks.

Despite NCCN's recommendation, more than 50% of H&N patients do not start postoperative RT within 6 weeks of their surgeries.[31] Many factors drive this delay, including clinical factors and social determinants of health.[32-34] A recent study evaluated the impact of numerous factors on treatment delays.[35] The authors concluded that low socioeconomic status, low levels of patient education, long travel times to treatment facilities, transition of care between multiple facilities, lack of insurance, advanced diseases requiring aggressive surgeries, complicated postoperative courses, delayed dental evaluations and extractions, and AA, Asian, or Hispanic ethnicities contribute to a delayed TSRT. Their finding concerning aggressive surgeries runs counter to our study, which showed no difference in the proportion of patients who received more extensive surgeries, including open surgeries and neck dissections, between the 2 TSRT ≤6 weeks and TSRT >6 weeks cohorts. Although our study was not designed to investigate the impact of aggressive surgeries on TSRT, our contrasting conclusion highlights the need for a future investigation to specifically elucidate this relationship.

The prolonged TSRT group was more likely to have a prolonged TTPT but similar RTT, indicating that TSRT mainly drives TTPT. Although our bivariate Cox PH regression models identified clinical/pathologic N stage as a possible predictor of RFS at $P < .10$, this conclusion did not hold for our full multivariable Cox PH regression model at $P < .05$. Other variables, including treatment facility, sex, age, smoking history, pathologic T stage, de-escalated RT (<56 Gy), omission or inclusion of chemotherapy, and TTPT (RTT could not be analyzed as no failures occurred in the prolonged RTT group), did not predict RFS in our bivariate or the multivariable Cox PH regression models. However, larger studies should explore these variables to clarify their impact or lack thereof on RFS more definitively.

This study has limitations typical of all retrospective analyses, including selection and reporting biases. Additionally, because of our restrictive inclusion criteria, the study cohort included only 96 patients. Of these, 31 patients experienced a prolonged TSRT, whereas 65 did not. This imbalance in the patients in each cohort may limit the generalizability of our conclusions. Whether our results can be reproduced for larger, more balanced cohorts remains to be seen. A small number of also meant that we had only 6 AA patients. Racial disparities in patient outcomes have been well characterized.[36] Thus, AA HPV+ OPSCC patients, unlike a mixed cohort, may be affected by the measures reported in our study, which should be explored in future studies. Furthermore, our small cohort constrains the statistical power of our study. Though the Kaplan-Meier curve generated herein illustrates a trend in TSRT, an investigation sufficiently powered to demonstrate these results is warranted. Lastly, although our cohorts were mostly well-balanced, the prolonged TSRT group had a lower proportion of current and former smokers and a higher percentage of never-smokers. Despite our bivariate and multivariate Cox PH regression models suggesting no impact of smoking history on treatment failure for our patients, the association between smoking and RFS should be explored in more extensive studies with cohorts exhibiting similar smoking histories, given the well-known association between smoking and treatment failure in other H&N cancers.

Our study adds to a growing body of evidence that establishes HPV+ OPSCCs as distinct cancers with significantly better outcomes that may not be governed by the traditional quality metrics, including TSRT, that impact

outcomes in HPV- tumors. These tumors also appear amenable to postsurgical treatment de-escalation without compromising oncologic outcomes. Strategies to de-escalate adjuvant treatment include reducing radiation dose and/or volumes and/or omitting chemotherapy. These emerging strategies make TORS more attractive for initial management.[28]

Our study indicates that prolonged TSRT may not adversely affect RFS for HPV + OPSCCs. Extending TSRT beyond the NCCN-recommended 6 weeks to allow for adequate postoperative convalescence may be another way to de-escalate treatment for these cancers, although the duration of extension which may be safe remains unknown. Large-scale randomized control trials evaluating oncologic outcomes and quality of life endpoints are needed to validate our findings and determine the optimal TSRT goal for HPV+ OPSCCs.

Conclusions

In this multi-institutional retrospective cohort study, TSRT >6 weeks was not statistically associated with inferior RFS in the postoperative management of HPV+ OPSCCs. These findings suggest that granting additional time to allow for adequate postoperative recovery for HPV+ OPSCCs before initiation of adjuvant therapies may not compromise oncologic outcomes. The TSRT goal for these cancers should be investigated in future studies.

Disclosures

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