Impact of Nonadherence to NCCN Adjuvant Radiotherapy Initiation Guidelines in Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population

Anusha Ponduri, BA^{1,*}; David Z. Liao, MD^{1,*}; Nicolas F. Schlecht, PhD^{2,3,4,†}; Gregory Rosenblatt, PhD²; Michael B. Prystowsky, MD, PhD²; Rafi Kabarriti, MD⁵; Madhur Garg, MD, MBA⁵; Thomas J. Ow, MD, MS^{2,6}; Bradley A. Schiff, MD⁶; Richard V. Smith, MD⁶; and Vikas Mehta, MD, MPH^{6,†}

ABSTRACT

Background: Nonadherence to NCCN Guidelines during time from surgery to postoperative radiotherapy (S-PORT) can alter survival outcomes in head and neck squamous cell carcinoma (HNSCC). There is a need to validate this impact in an underserved urban population and to understand risk factors and reasons for delay. We sought to investigate the impact of delayed PORT with outcomes of overall survival (OS) in HNSCC, to analyze predictive factors of delayed PORT, and to identify reasons for delay. **Methods:** We conducted a retrospective cohort study in an urban, community-based academic center. A total of 184 patients with primary HNSCC were identified through the Montefiore Medical Center cancer registry who had been treated between March 1, 2005, and March 8, 2017, and met the inclusion and exclusion criteria. The primary exposure was S-PORT. OS, recurrence, and risk factors and reasons for treatment delay were the main outcomes and measures. **Results:** Among 184 patients with HNSCC treated with PORT, the median S-PORT was 48.5 days (interquartile range, 41–67 days). The S-PORT threshold that optimally differentiated worse OS outcomes was >50 days (46.7% of our cohort; n=86). Independent of other relevant factors, patients with HNSCC and S-PORT >50 days had worse OS (hazard ratio, 2.30; 95% CI, 1.34–3.95) and greater recurrence (odds ratio, 3.51; 95% CI, 1.31–9.39). Predictors of delayed S-PORT included being underweight or obese, prolonged postoperative length of stay, and age >70 years. The most frequent reasons for PORT delay were complications related to surgery (22.09%), unrelated medical comorbidities (18.60%), and nonadherence/missed appointments (6.98%). **Conclusions:** Delayed PORT beyond 50 days after surgery was associated with decreased OS and greater recurrence. Identification of predictive factors and reasons for treatment delay helps to target at-risk patients and facilitates interventions in underserved populations.

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¹Albert Einstein College of Medicine, Bronx; ²Department of Pathology, and ³Department of Epidemiology & Population Health, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx; ⁴Department of Cancer Prevention & Control, Roswell Park Comprehensive Cancer Center, Buffalo; ⁵Department of Radiation Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx; and ⁶Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, Bronx, New York.

*These authors contributed equally and are co-first authors.

†These authors contributed equally as senior authors.

Background

Delays in delivery of care for head and neck squamous cell carcinoma (HNSCC) can increase risk of disease persistence or progression.^{1,2} Among the various delay intervals in HNSCC treatment, delayed time from surgery to postoperative radiotherapy (S-PORT) has been found to be significantly associated with increased mortality.^{3–10} Nonadherence to the NCCN recommendation of initiating postoperative radiotherapy (PORT) 6 weeks after surgery⁴ has been associated with decreased survival, and S-PORT times beyond 7 weeks may cause survival decrements with progressive time delay.⁸

Despite this evidence, HNSCC treatment in the United States has shown poor compliance with S-PORT recommendations in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Head and Neck Cancers.¹¹ A review of the National Cancer Database (NCDB) between 2006 and 2014 showed that >50% of patients with HNSCC who underwent curative-intent surgery with PORT did not start PORT within the recommended 6 weeks. Furthermore, the percentage of patients who received delayed PORT has increased over time. Failure to receive guideline-directed care has been associated with socioeconomic, oncologic, and hospital factors.¹² This is particularly pertinent to the socioeconomically disadvantaged patient population of Bronx, New York, where the mean per capita annual income is \$19,721.¹³

Although most studies show an association between delayed S-PORT and reduced survival, most of these are based on national cancer data registries, which are heterogeneous, do not analyze recurrence, and may not hold external validity in a local population. In addition, some of the studies have not shown a survival benefit of timely

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S-PORT.^{14–16} Recent advancements in intensity-modulated radiotherapy (RT), reduction of treatment time, and combining PORT with chemotherapy make the outcomes of delayed initiation uncertain.¹⁷ Reasons for S-PORT delay need to be investigated to identify susceptible patients and intervene in a prospective fashion. In this study, we sought to measure the impact of nonadherence to NCCN Guidelines on survival and disease recurrence in patients with HNSCC at a large urban health center, and investigated risk factors predictive of delay.

Methods

We identified 184 cases of primary adult HNSCC treated at an urban, community-based academic health center between March 1, 2005, and March 8, 2017. The study protocol was approved by the Institutional Review Board (IRB 2018-9739). Patients with HNSCC (including lip/oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and nose/sinuses) undergoing curative-intent surgery followed by PORT with or without chemotherapy were identified through the cancer registry. Exclusion criteria were stage IVC/metastatic cancer, noncurative palliative treatment, induction chemotherapy, chemotherapy alone, brachytherapy, or incomplete radiation history (see supplemental eFigure 1, available with this article at JNCCN.org).

S-PORT was defined as the number of days between ablative surgery and initiation of adjuvant treatment. An optimal S-PORT threshold was identified through recursive partitioning by using rpart version 4.1-13 (R Foundation for Statistical Computing), based on association with overall survival (OS). The threshold was validated by iterative Kaplan-Meier analysis for OS and comparisons between strata using log-rank tests at increasing S-PORT thresholds of 5 days. Cutoff was designated at the S-PORT time that showed the smallest *P* value after comparisons by log-rank test.

Multivariable Cox regression models were used to analyze the association between S-PORT delay and OS with adjustment for competing risk factors. The potential for confounding was examined for nonsignificant covariates using a change point estimate criterion for the association between S-PORT and OS.¹⁸ The proportional hazards assumptions were tested using log-log plots and Schoenfeld residuals. The association between S-PORT delay and recurrence was analyzed using multivariate logistic regression, because time-to-recurrence information was not available. Multivariable logistic regression analysis was also performed to identify risk factors for delayed S-PORT based on the identified threshold. Variable inflation factors were used to confirm the assumption of no multicollinearity. Time to treatment initiation (TTI) was defined as the time from diagnosis to the date of surgery. Staging was determined based on the 7th edition of

the *AJCC Cancer Staging Manual*. Adherence was defined as compliance with recommended therapy, including completion of recommended chemotherapy and RT at designated intervals. Completion of treatment was defined as completion without regard for how long treatment took to complete. Patients who did not complete the recommended therapy were censored at last observation or at time of death, if sooner. Covariates included in both multivariable models were selected based on a significance threshold of *P* < .05 in univariate analyses. Adjusted hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals were generated from the multivariable regression models using SPSS Statistics, version 25.0 (IBM Corp) and R (rpart, version 4.1-13; R Foundation for Statistical Computing) software. Chart reviews were performed to identify reasons for delay in S-PORT, and the reasons for treatment delay were categorized qualitatively.

Results

Population Characteristics

The study sample included 184 patients with HNSCC with a median follow-up of 37.5 months (interquartile range [IQR], 17–83 months). Median S-PORT time was 48.5 days (IQR, 41–67 days), whereas median surgical TTI was 36 days (IQR, 23.0–49.5 days). Recursive partitioning analysis and log-rank testing determined that the optimal S-PORT threshold to differentiate OS was >50 days. Almost half (*n* = 86; 46.7%) of the patients in the cohort had S-PORT >50 days and were classified as having delayed PORT.

Patient characteristics of our cohort are summarized in supplemental eTable 1. The most common primary tumor site was the lip/oral cavity (*n* = 84; 45.6%), and most patients (*n* = 114; 61.9%) were diagnosed with stage IV disease. Compared with patients with S-PORT ≤50 days, a greater proportion of those with S-PORT >50 days were 60 to 69 years of age (43% vs 23.5%; *P* = .042) and had a body mass index (BMI) <18.5 kg/m² (12.8% vs 4.1%; *P* = .056) or a BMI >30 kg/m² (22.1% vs 15.3%; *P* = .056). Patients with S-PORT >50 days were less likely to receive concurrent chemotherapy or cetuximab (38.4% vs 56.1%; *P* = .028), were more likely to have a 30-day postoperative readmission (25.6% vs 12.2%; *P* = .028), and were more likely to have a prolonged postoperative length of stay (LoS) of 8 to 30 days (46.5% vs 28.6%; *P* = .007) or >30 days (7.0% vs 4.1%; *P* = .007). Adherence to recommended therapy, including receiving concurrent chemotherapy based on NCCN Guidelines, was comparable in both the S-PORT ≤50 days (79.6%) and S-PORT >50 days (83.7%) groups.

Effect of S-PORT on Survival and Recurrence

Five-year OS was 66.4% for the entire cohort, 53.7% for those with S-PORT >50 days, and 77.5% for those with

S-PORT ≤ 50 days. The 5-year OS was 67.0% for the subset of patients with timely TTI based on the threshold of ≤ 60 days ($n=160$) previously determined by using rpart (version 4.1-13). Among patients with TTI ≤ 60 days, the 5-year OS was 51.8% for those with S-PORT >50 days and 78.0% for those with S-PORT ≤ 50 days. Among those with TTI >60 days, the 5-year OS was 57.3% for those with S-PORT >50 days and 71.1% for those with S-PORT ≤ 50 days.

Kaplan-Meier survival analysis showed a difference in the survival probabilities between patients with delayed S-PORT >50 days versus ≤ 50 days within the full cohort (log-rank $P=.006$) (Figure 1A) and among the subgroup of patients with TTI ≤ 60 days (log-rank $P=.012$) (Figure 1B). A strong association between survival and delayed S-PORT persisted after adjusting for prognostic factors in a multivariable Cox proportional hazards model including the full cohort (HR, 2.30; 95% CI, 1.34–3.95) and in the cohort restricted to patients with TTI ≤ 60 days (HR, 2.27; 95% CI, 1.25–4.11) (Table 1). TTI was not included as a covariate in survival analysis, because it was not shown to be a confounder of the association between S-PORT and OS as a categorical, continuous, or log-transformed variable (supplemental eTable 2).

The association between S-PORT time and OS was analyzed within subgroups defined by tumor site, stage, and adjuvant treatment modality (RT alone vs concurrent chemotherapy or cetuximab) (supplemental eTable 3). The association was most significant in patients with stage IV disease (HR, 2.21; 95% CI, 1.18–4.12) and in those with laryngeal cancer (HR, 4.78; 95% CI, 0.96–23.95). A less significant association was observed with S-PORT >50

days and OS in patients with p16-positive oropharyngeal cancer (HR, 2.44; 95% CI, 0.21–28.20) than in those with p16-negative or undetermined oropharyngeal cancer (HR, 10.81; 95% CI, 0.96–121.65). S-PORT >50 days was associated with significantly poorer OS only among patients who received RT without concurrent chemotherapy or cetuximab (HR, 5.80; 95% CI, 2.06–16.32). The association between S-PORT >50 days and OS in patients who received RT with concurrent chemotherapy or cetuximab was not significant (HR, 1.32; 95% CI, 0.62–2.79).

Logistic regression analysis was used to investigate risk of recurrence. Time to recurrence was not available for analysis, and we excluded 48 patients who were not assessed for recurrence at Montefiore Medical Center. After adjusting for other predictive factors of TTI >60 days, BMI, postoperative LoS, treatment adherence, and AJCC final stage, S-PORT >50 days (OR, 3.51; 95% CI, 1.31–9.39) and TTI >60 days (OR, 3.57; 95% CI, 1.05–12.19) were both associated with greater risk of recurrence (supplemental eTables 4 and 5). However, the association between delayed S-PORT and recurrence became nonsignificant after further excluding patients with unknown TTI, BMI, postoperative LoS, treatment adherence, or AJCC final stage.

Factors predictive of delayed S-PORT >50 days were explored using multivariable logistic regression (Table 2). BMI <18.5 kg/m² versus 18.5 to 30 kg/m² (OR, 3.98; 95% CI, 1.11–14.21) and postoperative LoS of 8 to 30 days versus 0 to 7 days (OR, 2.79; 95% CI, 1.36–5.74) were associated with increased odds of delayed S-PORT. Three other factors had borderline significant associations with delayed S-PORT: postoperative LoS >30

Figure 1. (A) Kaplan-Meier survival estimates based on a S-PORT threshold of 50 days among the entire cohort ($N=184$). Log-rank (Mantel-Cox) test chi-square, 7.64 ($P=.006$). Unadjusted HR for S-PORT >50 days, 2.06 (95% CI, 1.22–3.47). Adjusted hazard ratio for S-PORT >50 days, 2.30 (95% CI, 1.34–3.95). (B) Kaplan-Meier survival estimates based on S-PORT threshold of 50 days among patients with TTI ≤ 60 days ($n=160$). Log-rank (Mantel-Cox) test chi-square, 6.33 ($P=.012$). Unadjusted HR for S-PORT >50 days, 2.12 (95% CI, 1.22–3.68). Adjusted HR for S-PORT >50 days, 2.27 (95% CI, 1.25–4.11).

Abbreviations: HR, hazard ratio; S-PORT, time from surgery to postoperative radiotherapy; TTI, time to treatment initiation.

Table 1. Multivariate Cox Regression Models for Overall Survival

	All TTI (n=184) HR (95% CI)	TTI ≤60 d (n=160) HR (95% CI)
S-PORT >50 d	2.30 (1.34–3.95)	2.27 (1.25–4.11)
Adjuvant therapy adherence		
Nonadherent	Ref	Ref
Adherent	0.40 (0.22–0.72)	0.28 (0.15–0.52)
Unknown ^a	1.82 (0.23–14.66)	1.53 (0.19–12.53)
Tumor stage		
I–III	Ref	Ref
IV	2.14 (1.08–4.24)	1.94 (0.94–3.98)
Unknown ^b	4.10 (1.08–15.53)	2.64 (0.51–13.73)
Smoking		
Never	Ref	Ref
Current	2.48 (1.08–5.69)	2.78 (1.13–6.83)
Previous	1.82 (0.81–4.11)	1.90 (0.78–4.59)
Unknown ^c	3.29 (0.83–13.09)	4.53 (0.85–24.29)

The final model was adjusted for adjuvant therapy adherence, final stage according to the 7th edition of the *AJCC Cancer Staging Manual*, and smoking status. Excluding patients with “unknown” or “N/A” values for the covariates in the model did not result in significant changes (<10%) in HRs, as shown in supplemental eTable 4.

Abbreviations: HR, hazard ratio; N/A, not available; S-PORT, time from surgery to postoperative radiotherapy; TTI, time to treatment initiation.

^aData were unavailable for 1 patient for all TTI and 1 patient for TTI ≤60 d.

^bData were unavailable for 18 patients for all TTI and 17 patients for TTI ≤60 d.

^cData were unavailable for 6 patients for all TTI and 4 patients for TTI ≤60 d.

days versus 0 to 7 days (OR, 3.64; 95% CI, 0.85–15.52), age ≥70 versus <50 years (OR, 2.81; 95% CI, 0.97–8.02), and BMI >30 kg/m² versus 18.5 to 30 kg/m² (OR, 2.28; 95% CI, 0.98–5.29).

To identify individualized reasons for delayed S-PORT, medical charts of all patients with delayed S-PORT (n=86) were reviewed (Table 3). The median S-PORT time among these patients was 65.5 days (range, 51–369 days). The

Table 2. Multivariate Logistic Regression Model of Factors Potentially Predictive of Delayed S-PORT Based on Optimal Threshold of 50 Days

	OR (95% CI)
Postoperative LoS: 8–30 vs 0–7 d	2.79 (1.36–5.74)
Postoperative LoS: >30 vs 0–7 d	3.64 (0.85–15.52)
Age: ≥70 vs <50 y	2.81 (0.97–8.02)
BMI: >30 vs 18.5–30 kg/m ²	2.28 (0.98–5.29)
BMI: <18.5 vs 18.5–30 kg/m ²	3.98 (1.11–14.21)

Only statistically significant predictors are shown. The full regression model can be found in supplemental eTable 3. The final model was adjusted for postoperative LoS, age, and BMI.

Abbreviations: BMI, body mass index; LoS, length of stay; OR, odds ratio; S-PORT, time from surgery to postoperative radiotherapy.

Table 3. Reasons for Treatment Delay in Delayed S-PORT Cohort (n=86)

Reason	n (%)
Additional reconstruction needed	5 (5.81)
Changed treatment plan	1 (1.16)
Complications related to surgery	19 (22.09)
Nonadherence/Missed appointments	6 (6.98)
Persistent disease requiring reresection	2 (2.33)
Unrelated medical comorbidities	16 (18.60)
Unknown	37 (43.02)

Abbreviation: S-PORT, time from surgery to postoperative radiotherapy.

most common reason was surgical complications (n=19; 22.09%), including fistula (n=3), wound complications (n=7), and deconditioning (n=2). Another reason for delay was medical reasons related to patient comorbidities and hospital-acquired infections (n=16; 18.60%), including pneumonia, nephrolithiasis, stroke, hemoperitoneum, lung mass surgery, and arrhythmias. Treatment-associated reasons for delay included nonadherence to or missed appointments (n=6; 6.98%), additional reconstruction (n=5; 5.81%), persistent disease requiring reresection (n=2; 2.33%), and changed treatment plan (n=1; 1.16%).

Discussion

We investigated the impact of and reasons for nonadherence to NCCN Guidelines in S-PORT initiation for patients with HNSCC treated at an urban academic institution. When controlling for other influential factors, S-PORT >50 days corresponded to increased risk of recurrence and poorer OS. Regression analyses identified several risk factors for delayed S-PORT, including prolonged postoperative LoS (≥8 days), being underweight (BMI <18.5 kg/m²) or obese (BMI >30 kg/m²), and advanced age (≥70 years). Individualized reasons for S-PORT delay, including those related and unrelated to treatment, were also identified through chart review.

Although we previously established a negative impact of delayed surgical TTI on survival for patients with HNSCC independent of type of primary treatment,¹⁸ we found no independent association between TTI and survival within this cohort of patients with HNSCC receiving surgery with adjuvant RT. This result was consistent with a recent institutional study that found delayed treatment initiation did not impact survival in patients with HNSCC undergoing RT.¹⁹ The impact of S-PORT on survival was not confounded by TTI, and no significant association between delayed TTI and delayed S-PORT was identified, suggesting that the 2 delay intervals were independent. However, delayed TTI was found to be associated with greater recurrence.

Most studies assessing delayed S-PORT in the United States have been based on national cancer registries. Three of 4 NCDB studies demonstrated that S-PORT delay beyond the NCCN-recommended 6 weeks correlated with worse survival.^{3,5,8,10} Another study used restricted cubic splines to demonstrate that S-PORT >40 days significantly impacted mortality, with each delay beyond this increasing mortality until 70 days postoperatively.⁷ Although national cancer registries provide large sample sizes for statistical power, they lack recurrence data and contain a heterogeneous population that may not correspond with institutional experiences. In addition, factors in delay cannot be easily evaluated through registry data. To facilitate future interventions, we therefore sought to validate the findings from national cancer registries in our population and to identify reasons for delay.

Two-thirds (69.6%; $n=128$) of our patients were considered to have received delayed S-PORT based on the NCCN recommendation of initiating PORT ≤ 6 weeks after surgery.⁴ This was greater than the 55.3% of patients with S-PORT >6 weeks reported from NCDB data⁷ and may reflect the vulnerability of our population. Based on our recursive partitioning determined threshold of 50 days, 46.7% ($n=86$) of our patients experienced treatment delay, which was a slightly more lenient categorization of “delay” than the recommended NCCN definition.

Some studies have found delayed RT to have deleterious effects at different time points based on HNSCC stage. Fortin et al²⁰ demonstrated that delayed RT for >30 days was associated with poorer outcomes in the T2N0 subgroup and that a delay >40 days was associated with increased risk of local failure in their institutional cohort. Although nonadherence to NCCN Guidelines contributes to poorer survival, the exact timing of S-PORT may differ institutionally. Contrary to this study by Fortin et al, our analysis found that the association between S-PORT and OS was most relevant for patients with advanced-stage disease (stage IV). Our subgroup analysis also showed that the association with S-PORT delay was most significant among those receiving RT only, without concurrent chemotherapy or cetuximab. Some studies have shown mitigation of adverse effects of delay with chemotherapy, although no consensus exists.¹⁷ Thus, further inquiry may elucidate the role of chemotherapy in PORT delay.

Studies that did not find associations between S-PORT and OS have been based on small, single-institution cohorts; used arbitrary intervals instead of the NCCN recommendation of <6 weeks; and/or focused only on specific HNSCC subsites. Tumati et al¹⁴ found delay in TTI, but not S-PORT, to be associated with lower survival in a single-institution report, using an S-PORT threshold determined by the 75th percentile among their cohort (67 days). Studies of RT delay for patients with oral cavity cancer failed to find an association between S-PORT delay

and survival,^{15,16} in line with our study, which also found S-PORT delay not to be significantly associated with survival among patients with oral cavity cancer (HR, 1.22; 95% CI, 0.58–2.59). Other studies looking at specific tumor subsites found associations between delayed S-PORT and survival to be significant for laryngeal cancer⁶ and sinonasal cancer.⁹ We also found that the impact of delayed S-PORT on survival among patients with HPV/p16-positive oropharyngeal cancer was not significant, which is consistent with most prior studies.^{21–23} However, in an NCDB study of oropharyngeal cancer, Goel et al²⁴ found that delayed S-PORT based on a 40-day threshold was associated with survival, regardless of p16 status.

Most studies using national cancer databases do not study the impact of treatment delay on recurrence. Although we were able to demonstrate that delayed S-PORT >50 days and TTI >60 days were both associated with recurrence in multivariable analyses, only delayed TTI remained significant during sensitivity analysis excluding patients with unknown variables. This may be a statistical artifact due to small sample size and requires further investigation with larger institutional cohorts. Another recent institutional cohort study showed a significant association between delayed S-PORT >6 weeks and recurrence-free survival, but not OS, in patients with oral cancer.¹⁶ A meta-analysis of 20 institutional studies conducted before 2005 showed that local control worsened with increased RT waiting time in multiple oncologic settings, including HNSCC.²⁵

There has been less research on the predictors of treatment delay in HNSCC, especially among underserved and minority populations. We found that extended postoperative LoS, older age (≥ 70 years), and underweight and obese patients were more likely to have delayed S-PORT. Extended LoS intuitively would delay the initiation of adjuvant therapy. Patients with underweight BMI may be sarcopenic, which leads to increased postoperative complications.²⁶ Being underweight at diagnosis has been shown as an independent, adverse prognostic factor in HNSCC, whereas overweight BMI has conferred improved outcomes.²⁷ Underweight BMI was found to be a predictor of delayed TTI at our institution, suggesting that BMI may play a role in multiple intervals of treatment delays.¹⁸ Underweight BMI may predispose patients to deconditioning, which was a complication associated with delayed S-PORT. Overweight patients have also shown significantly better OS than normal-weight patients, independent of comorbidities, at our institution.²⁸ In contrast to a previous analysis that found diagnosis at a different institution to be associated with delayed TTI,¹⁸ we found no significant association between the location of diagnosis and delayed S-PORT. Finally, a recent institutional cohort study showed that African American patients had an absolute increase in the rate of PORT relative to White patients.²⁹ We found no significant association between

race and PORT delay, which may be secondary to our institution's primarily serving minorities (43% cohort) and to our limited sample size.

Exploring individualized reasons for delayed S-PORT in our cohort may elucidate areas for intervention. The most common reason was complications related to surgery, whereas other recurrent reasons included unrelated medical reasons and nonadherence. Better understanding of these reasons and implementing solutions will require a quality improvement approach that involves establishing treatment timelines, interviews, and education. An intervention targeting delayed dental evaluation, radiation oncology consults, and patient engagement has been used to successfully reduce RT initiation delay.³⁰ Another study found that early extractions were significantly associated with decreased risk of delay.³¹ Finally, a recent study found that patients undergoing RT consultation before surgery were 9 times more likely to receive timely PORT, and <10 days between surgery and RT referral made timely PORT 10 times more likely.²⁹

Because this was a retrospective study, accuracy was limited by patient records in which miscoding errors may have been present. The rareness of this tumor limited the study sample size and power. Furthermore, missing data in patient records were more likely for earlier cases, when electronic health records were unavailable. We opted not to impute missing values, because our data did not satisfy the missing-at-random assumption. Although the single-institution nature of this study may provide insight into the role of treatment delay in the setting of an underserved population at an urban medical center, it may be less generalizable to other populations. Because of missing time-to-recurrence information, we were unable to analyze recurrence using Cox regression. We were also unable to capture pathologic results, which increases the potential for confounding bias. However, the use of postoperative chemoradiation in the management of patients in this cohort partially serves as a surrogate marker for adverse pathologic features. Surgery type was also not available, and we controlled for T staging.

Although T staging does not always correlate with exact size, minimally invasive surgeries are rarely performed for those tumors that are T3. Thus, T staging was deemed a reasonable surrogate for this variable.

Conclusions

Our study findings showed that delayed PORT beyond 50 days after surgery was associated with decreased OS and greater recurrence. The association between delayed S-PORT and OS was most significant in patients with stage IV disease, with laryngeal cancer, or receiving radiotherapy only, without concurrent chemotherapy or cetuximab. We also found that the impact of S-PORT on OS in HPV/p16-positive oropharyngeal cancer was not significant. Postoperative LoS, age >70 years, and underweight and obese BMIs were associated with delayed S-PORT. Identification of predictive factors and reasons for treatment delay will help target at-risk patients and facilitate interventions in underserved populations.

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Correspondence: Vikas Mehta, MD, MPH, Department of Otorhinolaryngology–Head and Neck Surgery, Montefiore Medical Center, 3400 Bainbridge Avenue, 3rd Floor, MAP Building, Bronx, NY 10467. Email: dr.vikasmehtha@gmail.com

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Impact of Nonadherence to NCCN Adjuvant Radiotherapy Initiation Guidelines in Head and Neck Squamous Cell Carcinoma in an Underserved Urban Population

Anusha Ponduri, BA; David Z. Liao, MD; Nicolas F. Schlecht, PhD; Gregory Rosenblatt, PhD;
Michael B. Prystowsky, MD, PhD; Rafi Kabarriti, MD; Madhur Garg, MD, MBA; Thomas J. Ow, MD, MS;
Bradley A. Schiff, MD; Richard V. Smith, MD; and Vikas Mehta, MD, MPH

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eFigure 1: Diagram of Cohort Creation With Exclusion Criteria

eTable 1: Patient Characteristics Based on S-PORT Threshold of 50 Days

eTable 2: Multivariate Cox Regression Analysis for Overall Survival

eTable 3: Hazard Ratios for S-PORT >50 Versus ≤50 Days in Subgroup Analyses

eTable 4: Multivariate Logistic Regression Models for Recurrence

eTable 5: Full Multivariate Logistic Regression of Factors Predicting Delayed TTI Based on Optimal
Threshold of 60 Days

eFigure 1. Diagram of cohort creation with exclusion criteria.

eTable 1. Patient Characteristics Based on S-PORT Threshold of 50 Days

Characteristic	Total	Patients With S-PORT ≤50 d n (%)	Patients With S-PORT >50 d n (%)	Pearson Chi-Square	P Value
Total, n	184	98	86		
Sex				0.15	.70
Male	133	72 (73.5)	61 (70.9)		
Female	51	26 (26.5)	25 (29.1)		
Age				8.22	.042
<50 y	24	14 (14.3)	10 (11.6)		
50–59 y	49	31 (31.6)	18 (20.9)		
60–69 y	60	23 (23.5)	37 (43.0)		
≥70 y	51	30 (30.6)	21 (24.4)		
BMI				7.57	.056
>30 kg/m ²	34	15 (15.3)	19 (22.1)		
18.5–30 kg/m ²	122	70 (71.4)	52 (60.5)		
<18.5 kg/m ²	15	4 (4.1)	11 (12.8)		
Unknown	13	9 (9.2)	4 (4.7)		
Race/Ethnicity				6.33	.18
Hispanic	49	24 (24.5)	25 (29.1)		
African American	44	18 (18.4)	26 (30.2)		
Non-Hispanic White	44	25 (25.5)	19 (22.1)		
Unknown	47	31 (31.6)	16 (18.6)		
Language				1.34	.51
English	142	77 (78.6)	65 (75.6)		
Non-English	38	20 (20.4)	18 (20.9)		
Unknown	4	1 (1.0)	3 (3.5)		
Insurance				2.36	.80
Medicaid	54	29 (29.6)	25 (29.1)		
Medicare	64	33 (33.7)	31 (36.0)		
Commercial	35	21 (21.4)	14 (16.3)		
Self-pay	1	1 (1.0)	0 (0.0)		
N/A	3	1 (1.0)	2 (2.3)		
Other	27	13 (13.3)	14 (16.3)		
Socioeconomic status ^a				4.71	.32
First quartile: <−6.36	44	21 (21.4)	23 (26.7)		
Second quartile: −6.36 to −2.10	44	23 (23.5)	21 (24.4)		
Third quartile: −2.11 to −0.76	44	20 (20.4)	24 (27.9)		
Fourth quartile: >−0.76	43	28 (28.6)	15 (17.5)		
N/A	9	6 (96.1)	3 (3.5)		
Diagnosis at different institute				2.25	.13
No	77	36 (36.7)	41 (47.7)		
Yes	107	62 (63.3)	45 (52.3)		
CCI score				0.03	.99
0	156	83 (84.7)	73 (84.9)		
1	4	2 (2.0)	2 (2.3)		
≥2	24	13 (13.3)	11 (12.8)		

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eTable 1. Patient Characteristics Based on S-PORT Threshold of 50 Days (cont.)					
Characteristic	Total	Patients With S-PORT ≤50 d n (%)	Patients With S-PORT >50 d n (%)	Pearson Chi-Square	P Value
Tobacco use				1.78	.62
Current	66	38 (38.8)	28 (32.6)		
Previous	71	38 (38.8)	33 (38.4)		
Never	41	20 (20.4)	21 (24.4)		
Unknown	6	2 (2.0)	4 (4.7)		
Tumor site				7.72	.26
Oral	84	41 (41.8)	43 (50.0)		
Oropharynx	46	32 (32.7)	14 (16.3)	5.16	.076 ^b
p16+	23	15 (46.9)	8 (57.1)		
p16–	9	9 (28.1)	0 (0.0)		
Unknown	14	8 (25.0)	6 (42.9)		
Hypopharynx	5	3 (3.1)	2 (2.3)		
Larynx	33	14 (14.3)	19 (22.1)		
Nasopharynx	2	1 (1.0)	1 (1.2)		
Nasal/Sinus	11	5 (5.1)	6 (7.0)		
Other	3	2 (2.0)	1 (1.2)		
Marital status				1.35	.25
Married	57	34 (34.7)	23 (26.7)		
Unmarried	127	64 (65.3)	63 (73.3)		
AJCC stage (7th edition)				2.24	.70
I	9	3 (3.1)	6 (7.0)		
II	9	6 (6.1)	3 (3.5)		
III	34	19 (19.4)	15 (17.4)		
IV	114	60 (61.2)	54 (62.8)		
Unknown	18	10 (10.2)	8 (9.3)		
T stage				8.28	.082
T1	35	17 (17.3)	18 (20.9)		
T2	53	36 (36.7)	17 (19.8)		
T3	22	12 (12.2)	10 (11.6)		
T4	56	23 (23.5)	33 (38.4)		
Unknown	18	10 (10.2)	8 (9.3)		
N stage				5.48	.24
N0	52	21 (21.4)	31 (36.0)		
N1	34	20 (20.4)	14 (16.3)		
N2	77	45 (45.9)	32 (37.2)		
N3	4	3 (3.1)	1 (1.2)		
Unknown	17	9 (9.2)	8 (9.3)		
Concurrent chemotherapy or cetuximab				7.16	.028
Yes	88	55 (56.1)	33 (38.4)		
No	88	41 (41.8)	47 (54.7)		
Unknown	8	2 (2.0)	6 (7.0)		
Treatment completion				1.05	.59
Yes	149	79 (80.6)	70 (81.4)		
No	7	5 (5.1)	2 (2.3)		
N/A	28	14 (14.3)	14 (16.3)		

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eTable 1. Patient Characteristics Based on S-PORT Threshold of 50 Days (cont.)

Characteristic	Total	Patients With S-PORT ≤50 d n (%)	Patients With S-PORT >50 d n (%)	Pearson Chi-Square	P Value
Adherent to recommended treatment				0.52	.47
Yes	150	78 (79.6)	72 (83.7)		
No	34	20 (20.4)	14 (16.3)		
30-d readmission				7.12	.028
Yes	34	12 (12.2)	22 (25.6)		
No	120	72 (73.5)	48 (55.8)		
Unknown	30	14 (14.3)	16 (18.6)		
Postoperative LoS				12.24	.007
0–7 d	76	52 (53.1)	24 (27.9)		
8–30 d	68	28 (28.6)	40 (46.5)		
>30 d	10	4 (4.1)	6 (7.0)		
Unknown	30	14 (14.3)	16 (18.6)		
Time to treatment initiation				2.75	.097
>60 d	24	9 (9.2)	15 (17.4)		
≤60 d	160	89 (90.8)	71 (82.6)		
Date of diagnosis				0.04	.981
1/1/2005–12/31/2009	70	37 (52.9)	33 (47.2)		
1/1/2010–12/31/2014	83	44 (53.0)	39 (47.0)		
1/1/2015–present	31	17 (54.8)	14 (45.2)		

Bold indicates statistically significant P value.

Abbreviations: BMI, body mass index; CCI, Charlson-Deyo comorbidity index; LoS, length of stay; N/A, not available; S-PORT, time from surgery to postoperative radiotherapy.

^aQuartiles were determined by method outlined by Diez Roux et al.¹ Quartiles were determined by patient's address, geocoded to a census block, with a neighborhood SES score determined. Each quartile score reflects the number of standard deviations from the mean SES score of NY census blocks.

^bP value based on chi-square test of p16 status among patients with oropharyngeal cancer.

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eTable 2. Multivariate Cox Regression Analysis for Overall Survival

Cox Regression for OS: TTI as Log-Transformed Variable	
HR (95% CI)	
TTI as categorical variable	
S-PORT >50 d	2.32 (1.31–4.14)
TTI >60 d	1.11 (0.55–2.26)
Adjuvant therapy adherence	
Adherent	Ref
Nonadherent	2.44 (1.28–4.65)
Unknown	4.26 (0.54–33.71)
Tumor stage	
I–III	Ref
IV	2.60 (1.21–5.61)
Unknown	2.31 (0.27–19.72)
Smoking	
Current	Ref
Never	0.55 (0.24–1.25)
Previous	0.77 (0.41–1.45)
Unknown	1.45 (0.28–7.57)
TTI as continuous variable	
S-PORT >50 d	2.34 (1.30–4.22)
TTI (continuous)	1.00 (0.99–1.01)
Adjuvant therapy adherence	
Nonadherent	Ref
Adherent	0.41 (0.21–0.78)
Unknown	1.71 (0.20–14.40)
Tumor stage	
I–III	Ref
IV	2.62 (1.22–5.63)
Unknown	2.35 (0.28–20.06)
Smoking	
Current	Ref
Never	0.54 (0.24–1.24)
Previous	0.77 (0.41–1.43)
Unknown	1.53 (0.31–7.66)

(continued)

eTable 2. Multivariate Cox Regression Analysis for Overall Survival (cont.)

Cox Regression for OS: TTI as Log-Transformed Variable	
HR (95% CI)	
TTI as log-transformed variable	
S-PORT >50 d	2.28 (1.27–4.11)
Log (TTI)	1.09 (0.73–1.63)
Adjuvant therapy adherence	
Nonadherent	Ref
Adherent	0.41 (0.22–0.79)
Unknown	1.84 (0.22–15.50)
Tumor stage	
I–III	Ref
IV	2.62 (1.22–5.64)
Unknown	2.33 (0.27–19.82)
Smoking	
Current	Ref
Never	0.55 (0.24–1.25)
Previous	0.77 (0.41–1.44)
Unknown	1.55 (0.31–7.73)

Models were generated with TTI as a categorical variable (>60 vs ≤60 days), continuous variable, and log-transformed variable.

Abbreviations: HR, hazard ratio; OS, overall survival; S-PORT, time from surgery to postoperative radiotherapy; TTI, time to treatment initiation.

eTable 3. Hazard Ratios for S-PORT >50 Versus ≤ 50 Days in Subgroup Analyses	
	HR (95% CI)
Tumor site	
Larynx	4.78 (0.96–23.95)
Oropharynx	3.44 (0.67–17.58)
Lip/Oral	1.22 (0.58–2.59)
Other ^a	2.36 (0.36–15.38)
p16 status	
p16+ OPC	2.44 (0.21–28.20)
p16– or unknown OPC	10.81 (0.96–121.65)
p16– or unknown (any site)	2.31 (1.32–4.05)
Concurrent chemotherapy or cetuximab	
Yes	1.32 (0.62–2.79)
No	5.80 (2.06–16.32)
Final tumor stage	
I–III	2.41 (0.67–8.65)
IV	2.21 (1.18–4.12)

HRs are adjusted for the remainder covariates in the multivariate Cox regression in Table 3.
Abbreviations: HR, hazard ratio; OPC, oropharyngeal cancer; S-PORT, time from surgery to postoperative radiotherapy.
^aNasopharynx, nasal, hypopharynx, other.

eTable 4. Multivariate Logistic Regression Models for Recurrence

	Recurrence OR (95% CI)	Recurrence Excluding Unknowns OR (95% CI)
S-PORT >50 d	3.51 (1.31–9.39)	1.66 (0.51–5.40)
TTI >60 d	3.57 (1.05–12.19)	3.51 (1.25–19.42)
BMI category		
18.5–30 kg/m ²	Ref	Ref
<18.5 kg/m ²	0.73 (0.09–5.63)	0.94 (0.12–7.62)
>30 kg/m ²	4.1 (1.38–12.16)	7.91 (2.03–30.87)
Unknown ^a	4.33 (0.674–27.81)	
Postoperative LoS	1.94 (0.94–3.98)	
0–7 d	Ref	Ref
8–30 d	2.64 (0.51–13.73)	7.08 (1.70–29.55)
>30 d	1.26 (0.10–16.11)	5.34 (0.32–89.30)
Unknown ^b	4.38 (0.87–22.10)	
Adherent to treatment	0.09 (0.03–0.34)	0.05 (0.01–0.24)
Tumor stage		
I–III	Ref	Ref
IV	1.51 (0.54–4.22)	0.72 (0.22–2.41)
Unknown ^c	1.08 (0.19–6.09)	

Models were generated that included and excluded patients with unknown covariate values. The final model was adjusted for TTI >60 days, BMI, postoperative LoS, treatment adherence, and AJCC final stage.

Abbreviations: BMI, body mass index; LoS, length of stay; OR, odds ratio; S-PORT, time from surgery to postoperative radiotherapy; TTI, time to treatment initiation.

^a7 patients had unknown BMI.

^b12 patients had unknown postoperative LoS.

^c15 patients had unknown stage.

eTable 5. Full Multivariate Logistic Regression of Factors Predicting Delayed TTI Based on Optimal Threshold of 60 Days	
	OR (95% CI)
BMI category	
18.5–30 kg/m ²	Ref
<18.5 kg/m ²	3.98 (1.11–14.21)
>30 kg/m ²	2.28 (0.98–5.29)
N/A	0.57 (0.16–2.12)
Postoperative LoS	
0–7 d	Ref
8–30 d	2.79 (1.36–5.74)
>30 d	3.64 (0.85–15.52)
N/A	3.41 (1.33–8.73)
Age	
<50 y	Ref
50–59 y	1.03 (0.36–2.96)
60–69 y	0.91 (0.31–2.65)
≥70 y	2.81 (0.99–8.02)

Abbreviations: BMI, body mass index; LoS, length of stay; N/A, not available; OR, odds ratio; TTI, time to treatment initiation.