Original Article

Effect of Time to Initiation of Postoperative Radiation Therapy on Survival in Surgically Managed Head and Neck Cancer

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BACKGROUND: The objective of this study was to determine the effects of National Comprehensive Cancer Network (NCCN) guideline–adherent initiation of postoperative radiation therapy (PORT) and different time-to-PORT intervals on the overall survival (OS) of patients with head and neck squamous cell carcinoma (HNSCC). **METHODS:** The National Cancer Data Base was reviewed for the period of 2006-2014, and patients with HNSCC undergoing surgery and PORT were identified. Kaplan-Meier survival estimates, Cox regression analysis, and propensity score matching were used to determine the effects of initiating PORT within 6 weeks of surgery and different time-to-PORT intervals on survival. **RESULTS:** This study included 41,291 patients. After adjustments for covariates, starting PORT >6 weeks postoperatively was associated with decreased OS (adjusted hazard ratio [aHR], 1.13; 99% confidence interval [CI], 1.08-1.19). This finding remained in the propensity score–matched subset (hazard ratio, 1.21; 99% CI, 1.15-1.28). In comparison with starting PORT 5 to 6 weeks postoperatively, initiating PORT earlier was not associated with improved survival (aHR for ≤4 weeks, 0.93; 99% CI, 0.85-1.02; aHR for 4-5 weeks, 0.92; 99% CI, 0.84-1.01). Increasing durations of delay beyond 7 weeks were associated with small, progressive survival decrements (aHR, 1.09, 1.10, and 1.12 for 7-8, 8-10, and >10 weeks, respectively). **CONCLUSIONS:** Nonadherence to NCCN guidelines for initiating PORT within 6 weeks of surgery was associated with decreased survival. There was no survival benefit to initiating PORT earlier within the recommended 6-week timeframe. Increasing durations of delay beyond 7 weeks were associated with small, progressive survival decrements. ***Cancer*** **2017;123:4841-50.** *© 2017 American Cancer Society.*

KEYWORDS: head and neck cancer, National Comprehensive Cancer Network (NCCN) guidelines, National Cancer Data Base, postoperative radiation therapy, quality of care.

INTRODUCTION

Guideline-concordant treatment and timeliness of care are 2 indicators of quality care.[1-7] The only measure of timely care incorporated into National Comprehensive Cancer Network (NCCN) guidelines for patients with head and neck squamous cell carcinoma (HNSCC) is the time interval between surgery and postoperative radiation therapy (PORT), for which the "preferred interval between resection and postoperative RT is ≤6 weeks."[8] Delays in initiating adjuvant therapy and care not adherent to NCCN guidelines are nevertheless common.[9-12]

The oncologic effect of NCCN guideline–adherent care for timely adjuvant therapy remains uncertain.[13] Prior studies have shown inconsistent effects on locoregional recurrence and survival, with some finding a benefit[14-21] and others finding no influence.[10,11,22-26] Most of the studies finding a benefit from the earlier initiation of adjuvant therapy were conducted more than 15 years ago. It has been argued that recent improvements in radiation technology, such as intensity-modulated radiation therapy, altered fractionation, and concurrent chemotherapy, may mitigate against the risk associated with delays in initiating PORT,[13] although no consensus exists.

The effects of different times to the initiation of PORT on oncologic outcomes is also unknown. Some have argued, on the basis of tumor repopulation times and surgical effects on hypoxia, that the initiation of adjuvant therapy should commence as soon as it is reasonably achievable.[27] Whether there is a benefit to starting PORT earlier, such as within 4 or

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The National Cancer Data Base is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in the study are derived from a de-identified National Cancer Data Base file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data by the investigators.

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5 weeks of surgery, remains understudied. Conversely, the negative consequences of progressive delays beyond 6 weeks postoperatively are also unknown.

Given the uncertainty surrounding the effect of the time to the initiation of PORT for patients with HNSCC undergoing surgery and adjuvant therapy, we sought to answer the following questions: 1) is NCCN guideline–adherent care in which PORT is initiated within 6 weeks of surgery associated with improved overall survival (OS), 2) is there a survival benefit from earlier initiation of PORT, and 3) what effect do increasing durations of delay beyond 6 weeks in initiating PORT have on survival?

MATERIALS AND METHODS

Data Source

The National Cancer Data Base (NCDB) is a hospital-based cancer registry that is a joint program of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. The NCDB annually collects high-quality and internally appraised cancer data from more than 1500 CoC-accredited hospitals in the United States. It captures approximately 70% of cancer diagnoses annually in the United States, and this makes it the world's largest clinical cancer registry.[28]

Study Cohort

The institutional review board of the Medical University of South Carolina deemed this study exempt from review. The NCDB was reviewed from 2006 to 2014 for patients with upper aerodigestive tract HNSCC and no prior radiation who were undergoing curative-intent surgery followed by postoperative radiation with or without chemotherapy. HNSCC diagnoses were filtered with the *International Classification of Diseases for Oncology* (3rd edition) topography codes for the oral cavity (including the lip), oropharynx, hypopharynx, and larynx as well as histology codes for squamous cell carcinoma (SCC) or relevant variants (Supporting Table 1 [see online supporting information]). In all, 58,722 patients were identified. Patients were excluded for the following reasons: brachytherapy, stereotactic radiotherapy, radioisotopes, or unspecified modality (n = 568 for all forms of excluded radiation therapy); induction chemotherapy (n = 9896); palliative therapy (n = 437); unknown survival time (n = 6031); definitive surgery more than 180 days after the diagnosis (n = 129); and initiation of PORT more than 180 days after the surgery (n = 370).

Outcome Measures

The primary outcome measure was OS, which was calculated as the time from the date of diagnosis to the date of death or last follow-up. Tumor registrars report patient follow-up to the NCDB annually, and CoC accreditation standards require an annual 90% follow-up rate for all living analytic patients.[29] Neither patterns of failure nor disease-specific survival is available in the NCDB.

Study Variables

Covariates included the sociodemographics (age, sex, race, educational attainment, and median household income), insurance type, severity of comorbidities, oncologic characteristics (tumor site and American Joint Committee on Cancer clinical and pathologic stages), and treatment characteristics (surgical margins, number of lymph nodes removed, 30-day hospital readmission, time to PORT, radiation modality, radiation duration, radiation dose, administration of concurrent chemotherapy, treatment facility type, treatment at more than 1 facility, surgery and radiation at the same facility, and region of the United States). Categorical variables were grouped for analysis as previously described.[9]

Statistical Analysis

To determine the effect of NCCN guideline–adherent care on OS, the time to the initiation of PORT was dichotomized into $\leq$6 weeks and >6 weeks postoperatively. Kaplan-Meier (KM) estimates of survival were used to examine unadjusted survival time distributions for patients who initiated PORT $\leq$6 weeks or > 6 weeks postoperatively; comparisons were performed with the log-rank test. Univariate and multivariate Cox proportional hazards regression analysis was performed to identify factors associated with OS and to make adjustments for potential confounding variables. The proportional hazards assumption was verified with log-minus-log plots. Associations between covariates were investigated before modeling to address potential collinearity effects. Variables significant at an α level of .05 in the univariate analysis with perceived clinical relevance were entered into the Cox multivariate regression model. For categorical variables with unknown or missing information, an unknown category was included throughout, but it was omitted from the presentation of the final multivariate analyses for clarity of presentation.

Propensity score matching (PSM) was used to minimize the effects of confounding from nonrandomized treatment assignment[30] and to decrease the bias between the cohorts that commenced adjuvant therapy within or

more than 6 weeks postoperatively. Individual scores based on the probability of starting PORT within 6 weeks of surgery were calculated via the fitting of a logistic regression model. One-to-one PSM without replacement was performed with a caliper width set to 0.05 times the standard deviation of the logit of the propensity score.[31,32] After PSM, the OS of patients who initiated PORT ≤6 weeks and >6 weeks postoperatively was examined with Kaplan-Meier estimates of survival and compared with the log-rank test. Unadjusted hazard ratios (HRs) for the PSM cohort were determined with Cox regression modeling.

Because of the biological and prognostic differences between carcinogen-mediated and human papillomavirus (HPV)–related head and neck cancer,[33,34] a planned subset analysis of the entire data set was performed that excluded patients with HPV-related oropharyngeal SCC. Collaborative Stage Site Specific Factor 10 codes 020 to 060 were used to exclude patients with high-risk HPV serotypes (n = 3656).[35] Because the HPV status was not recorded until 2010[35] but many patients from 2006 to 2010 likely had HPV-related oropharyngeal SCC with the HPV status coded as unknown, a second subset analysis excluding all patients with oropharyngeal SCC (n = 17,158) was performed to minimize this potential source of bias.

To determine whether an earlier time to the initiation of PORT is beneficial in terms of survival and whether increasing durations of delay beyond 6 weeks are associated with progressive decrements in survival, the time to PORT was analyzed as a categorical variable. Patients were divided into groups based on the time to the initiation of PORT: ≤4, 4 to 5, 5 to 6, 6 to 7, 7 to 8, 8 to 10, and >10 weeks (the intervals are not inclusive of the lower bound and are inclusive of the upper bound for each). The time to PORT was analyzed as a categorical variable instead of a continuous variable because of the easier clinical interpretation and application of the HRs. Univariate and multivariate Cox proportional hazards regression analyses were performed to make adjustments for confounders and to determine the effect of different time-to-PORT-initiation intervals on OS.

The data analysis was performed with SPSS 24 (IBM SPSS, Inc, Armonk, New York). All statistical tests were 2-sided. Because of the large sample size, statistical significance was set at a P value < .01, and measures of the precision of point estimates are presented as 99% confidence intervals (CIs).

RESULTS

Demographic, Clinicopathologic, and Treatment Characteristics

In all, 41,291 patients with HNSCC undergoing surgery and PORT from 2006 to 2014 were included in the study. The patient demographic, clinicopathologic, and treatment characteristics and their relation to the initiation of PORT within 6 weeks of surgery are presented in Table 1. There were numerous significant differences in the characteristics of the groups with and without timely postoperative radiation. Overall, 44.7% of the patients (n = 18,462) initiated PORT within 6 weeks of surgery.

Effect of Initiating PORT ≤6 Weeks Postoperatively on Survival

Initiating adjuvant therapy more than 6 weeks postoperatively was associated with a 10% absolute decrease in 5-year OS in unadjusted Kaplan-Meier estimates in comparison with initiating adjuvant radiation within 6 weeks of surgery (60.2% vs 70.8%; log-rank P < .001; Fig. 1). The results of the univariate and multivariate Cox regression analyses are shown in Table 2. In the univariate analysis, starting adjuvant therapy more than 6 weeks after surgery was associated with a 50% relative increase in mortality (HR, 1.48; 99% CI, 1.41-1.55). After adjustments for relevant covariates, commencing adjuvant therapy more than 6 weeks after surgery remained associated with decreased OS (adjusted hazard ratio [aHR], 1.13; 99% CI, 1.08-1.19).

Effect of Initiating PORT ≤6 Weeks Postoperatively on Survival in the Propensity Score–Matched Cohort

Because of the inherent imbalances in characteristics between the groups that did and did not start adjuvant therapy within 6 weeks of surgery,[9] a propensity score–adjusted subset analysis was performed on the basis of the likelihood of initiating PORT within 6 weeks of surgery (Supporting Table 2 [see online supporting information]). In the propensity score–matched cohort of 29,910 patients, initiating adjuvant therapy more than 6 weeks after surgery was associated with a 5% absolute decrease in 5-year OS in comparison with initiating adjuvant therapy within 6 weeks of surgery (64.3% vs 69.4%; log-rank P < .001; Fig. 2). According to univariate analyses, the initiation of adjuvant therapy more than 6 weeks after surgery was associated with a 20% relative increased risk of mortality (HR, 1.21; 99% CI, 1.15-1.28).

Subset Analysis Excluding High-Risk HPV-Related SCC and Oropharyngeal SCC

Because of the large survival differences among oropharynx cancer patients in this study and the known biological

TABLE 1. Demographic, Clinicopathologic, and Treatment Characteristics

Variable	Total Patients (n = 41,291), No. (%)	Initiation of PORT at ≤6 wk (n = 18,462), No. (%)	Initiation of PORT at >6 wk (n = 22,829), No. (%)	*P*
Age				<.001
<50 y	8474 (20.5)	3815 (20.7)	4659 (20.4)	
50-59 y	14,569 (35.3)	6323 (34.2)	8246 (36.1)	
60-69 y	11,195 (27.1)	4977 (27.0)	6218 (27.2)	
≥70 y	7053 (17.1)	3347 (18.1)	3706 (16.2)	
Sex				<.001
Male	31,194 (75.5)	14,378 (77.9)	16,816 (73.7)	
Female	10,097 (24.5)	4084 (22.1)	6013 (26.3)	
Race				<.001
White	36,234 (87.8)	16,608 (90.0)	19,626 (86.0)	
Black	3556 (8.6)	1279 (6.9)	2277 (10.0)	
Other/unknown	1501 (3.6)	575 (3.1)	926 (4.1)	
Insurance type				<.001
Private	20,292 (49.1)	9971 (54.0)	10,321 (45.2)	
Medicare	13,231 (32.0)	5884 (31.9)	7347 (32.2)	
Medicaid	4056 (9.8)	1240 (6.7)	2816 (12.3)	
Uninsured	2236 (5.4)	780 (4.2)	1456 (6.4)	
Other/unknown	1476 (3.6)	587 (3.1)	889 (2.3)	
Education				<.001
Highest quartile	9153 (22.2)	4565 (24.7)	4588 (20.1)	
2nd highest quartile	13,607 (33.0)	6136 (33.2)	7471 (32.7)	
2nd lowest quartile	11,096 (26.9)	4812 (26.1)	6284 (27.5)	
Lowest quartile	7022 (17.0)	2787 (15.1)	4235 (18.6)	
Unknown	413 (1.0)	162 (0.9)	251 (1.1)	
Median household income				<.001
Highest quartile	11,958 (29.0)	5667 (30.7)	6291 (27.6)	
2nd highest quartile	11,069 (26.8)	5023 (27.2)	6046 (26.5)	
2nd lowest quartile	10,235 (24.8)	4511 (24.4)	5724 (25.1)	
Lowest quartile	7589 (18.4)	3087 (16.7)	4502 (19.7)	
Unknown	440 (1.1)	174 (0.9)	266 (1.2)	
Charlson/Deyo comorbidity score				<.001
0	32,726 (79.3)	14,974 (81.1)	17,752 (77.8)	
1	6788 (16.4)	2794 (15.1)	3994 (17.5)	
≥2	1777 (4.3)	694 (3.8)	1083 (4.7)	
Cancer primary site				<.001
Oral cavity	13,007 (31.5)	3754 (20.3)	9253 (40.5)	
Oropharynx	17,158 (41.6)	8866 (48.0)	8292 (35.3)	
Hypopharynx	1093 (2.6)	397 (2.2)	696 (3.0)	
Larynx	10,033 (24.3)	5445 (29.5)	4588 (20.1)	
AJCC clinical stage grouping				<.001
I	5387 (13.0)	3304 (17.9)	2083 (9.1)	
II	5029 (12.2)	2336 (12.7)	2693 (11.8)	
III	6700 (16.2)	2958 (16.0)	3742 (16.4)	
IV	15,531 (37.6)	6127 (33.2)	9404 (41.2)	
Unknown	8644 (20.9)	3737 (20.2)	4907 (21.5)	
AJCC pathologic stage grouping				<.001
I	2766 (6.7)	1621 (8.8)	1145 (5.0)	
II	2922 (7.1)	1281 (6.9)	1641 (7.2)	
III	5483 (13.3)	2277 (12.3)	3206 (14.0)	
IV	18,083 (43.8)	6388 (34.6)	11,695 (51.2)	
Unknown	12,037 (29.2)	6895 (37.3)	5142 (22.5)	
Surgical margins				<.001
Negative	24,470 (59.3)	9461 (51.2)	15,009 (65.7)	
Positive	10,362 (25.1)	4991 (27.0)	5371 (23.5)	
Unknown	6459 (15.6)	4010 (21.7)	2449 (10.7)	
No. of lymph nodes removed				<.001
<18	7001 (17.0)	3050 (16.5)	3951 (17.3)	
≥18	17,714 (42.9)	5620 (30.4)	12,094 (53.0)	
Unknown	16,576 (40.1)	9792 (53.0)	6784 (29.7)	
30-d hospital readmission				<.001
None	37,027 (89.7)	16,785 (90.9)	20,242 (88.7)	
Unplanned	1196 (2.9)	420 (2.3)	776 (3.4)	
Planned	1129 (2.7)	483 (2.6)	646 (2.8)	
Unknown	1939 (4.7)	774 (4.2)	1165 (5.1)	

TABLE 1. *Continued*

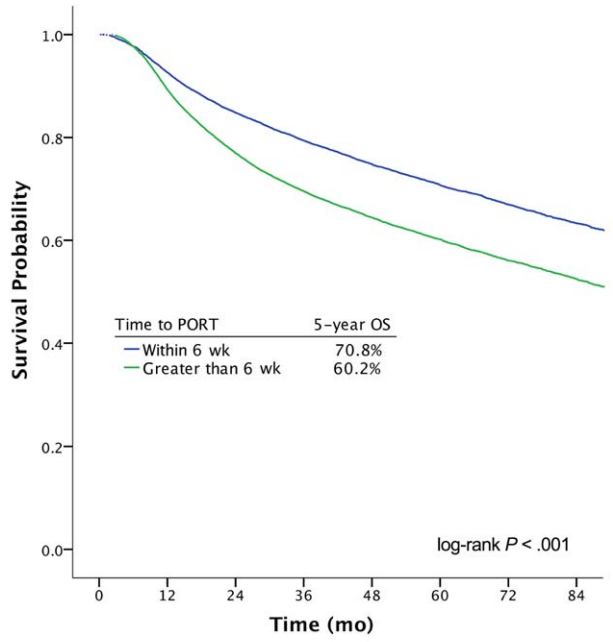
Variable	Total Patients (n = 41,291), No. (%)	Initiation of PORT at ≤6 wk (n = 18,462), No. (%)	Initiation of PORT at >6 wk (n = 22,829), No. (%)	*P*
Radiation modality[a]				<.001
External beam	18,301 (44.3)	8657 (46.9)	9644 (42.2)	
IMRT	21,426 (51.9)	8972 (48.6)	12,454 (54.6)	
3DCT	1511 (3.7)	825 (4.5)	686 (3.0)	
Concurrent chemoradiation				.701
No	19,035 (46.1)	8487 (46.0)	10,548 (46.2)	
Yes	21,876 (53.0)	9798 (53.1)	12,078 (52.9)	
Unknown	380 (0.9)	177 (1.0)	203 (0.9)	
Radiation dose				<.001
<40 Gy	2120 (5.1)	769 (4.2)	1351 (5.9)	
40-59.9 Gy	10,915 (26.4)	4568 (24.7)	6347 (27.8)	
60-66 Gy	16,780 (40.6)	7094 (38.4)	9686 (42.4)	
>66 Gy	8270 (20.0)	4618 (25.0)	3652 (16.0)	
Unknown	3206 (7.8)	1413 (7.7)	1793 (7.9)	
Radiation treatment duration				<.001
1-35 d	2528 (6.1)	766 (4.1)	1762 (7.7)	
36-42 d	5261 (12.7)	2471 (13.4)	2790 (12.2)	
43-49 d	15,179 (36.8)	6686 (36.2)	8493 (37.2)	
50-63 d	14,220 (34.4)	6765 (36.6)	7455 (32.7)	
≥64 d	4103 (9.9)	1774 (9.6)	2329 (10.2)	
Treatment facility type				<.001
Community	3571 (8.6)	1855 (10.0)	716 (7.5)	
Comprehensive community	14,561 (35.3)	7372 (39.9)	7189 (31.5)	
Academic	17,842 (43.2)	6281 (36.9)	11,021 (48.3)	
Integrated network	4078 (9.9)	1853 (10.0)	2225 (9.7)	
Other/unknown	1239 (3.0)	561 (3.0)	678 (3.0)	
No. of treatment facilities				<.001
1 CoC facility	8974 (21.7)	4099 (22.2)	4875 (21.4)	
>1 CoC facility	9970 (24.1)	4108 (22.3)	5862 (25.7)	
Unknown	22,347 (54.1)	10,255 (55.5)	12,092 (53.0)	
Surgery and radiation at same facility				<.001
Yes	20,317 (49.2)	9693 (52.5)	10,624 (46.5)	
No	20,974 (50.8)	8769 (47.5)	12,205 (53.5)	
Region of United States				<.001
East	7838 (19.0)	3102 (16.8)	4736 (20.7)	
Central	11,912 (28.8)	5660 (30.7)	6252 (27.4)	
South	14,340 (34.7)	6551 (35.5)	7789 (34.1)	
West	5962 (14.4)	2588 (14.0)	3374 (14.8)	
Unknown	1239 (3.0)	561 (3.0)	678 (3.0)	

Abbreviations: 3DCT, 3-dimensional conformal therapy; AJCC, American Joint Committee on Cancer; CoC, Commission on Cancer; IMRT, intensity-modulated radiation therapy; PORT, postoperative radiation therapy.
[a] To protect patient identity in accordance with National Cancer Data Base policy, certain rows/columns may not add up to the total for cases in which 1 of the categorical variables has a cell size < 10.

and prognostic differences between carcinogen-mediated and HPV-related HNSCC,[33,34] a subset analysis of the entire data set was performed that excluded patients with high-risk HPV-positive oropharyngeal carcinoma. After the exclusion of patients with high-risk HPV-positive oropharyngeal carcinoma and adjustments for relevant covariates, starting adjuvant therapy more than 6 weeks after surgery remained associated with an increased risk of death (aHR, 1.13; 99% CI, 1.08-1.19; Supporting Table 3 [see online supporting information]). In a second subset analysis of the entire data set excluding all oropharyngeal SCC patients, the risk of mortality from initiating PORT more than 6 weeks after surgery was unchanged in the multivariate analysis (aHR, 1.09; 99% CI, 1.03-1.15; Supporting Table 4 [see online supporting information]).

Effect of Increasing the Time to the Initiation of PORT on Survival

To determine whether an earlier time to the initiation of PORT was beneficial in terms of OS and whether increasing durations of delay beyond 6 weeks were associated with larger decrements in survival, the time to the initiation of adjuvant therapy was analyzed as a categorical variable: 15.7% (n = 6494) started PORT ≤ 4 weeks after surgery, 13.6% (n = 5635) started PORT 4 to 5 weeks after surgery, 15.3% (n = 6333) started PORT 5 to 6



	No. at Risk							
	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo
PORT at ≤6 wk	18,462	16,438	13,517	10,527	8017	5772	3878	2453
PORT at >6 wk	22,829	19,727	15,035	11,152	8242	5816	3801	2313

Figure 1. Kaplan-Meier estimates of OS demonstrating the effect of NCCN guideline–adherent initiation of PORT within 6 weeks of surgery versus non–guideline-adherent care initiating PORT more than 6 weeks postoperatively (n = 41,291). NCCN indicates National Comprehensive Cancer Network; OS, overall survival; PORT, postoperative radiation therapy.

weeks after surgery, 14.6% (n = 6015) started PORT 6 to 7 weeks after surgery, 11.3% (n = 4685) started PORT 7 to 8 weeks after surgery, 5515 (13.4%) started PORT 8 to 10 weeks after surgery, and 16.0% (n = 6614) started PORT > 10 weeks after surgery (the time intervals are inclusive of the upper bound for each). The Kaplan-Meier estimates of OS with different times to the initiation of adjuvant therapy are shown in Figure 3. In comparison with starting PORT 5 to 6 weeks after surgery, initiating adjuvant therapy ≤4 weeks after surgery and 4 to5 weeks after surgery was associated with significant improvements in OS in the univariate analysis (HR for PORT at ≤4 weeks postoperatively, 0.84; 99% CI, 0.77-0.92; HR for PORT at 4-5 weeks postoperatively, 0.84; 99% CI, 0.76-0.92). In the univariate analysis, increasing durations of delay beyond 6 weeks were associated with progressively larger decreases in OS (HR for 6-7 weeks, 1.15; 99% CI, 1.06-1.25; HR for 7-8 weeks, 1.26; 99% CI, 1.16-1.38; HR for 8-10 weeks, 1.39; 99% CI, 1.28-1.51; HR for > 10 weeks, 1.46; 99% CI, 1.35-1.58). Importantly, the earlier commencement of adjuvant therapy did not remain associated with improved OS in the multivariate analysis adjusted for relevant covariates (Fig. 4). Increasing durations of delay beyond 7 weeks postoperatively remained associated with small, progressive decrements in OS in the multivariate analysis (aHR for 7-8 weeks, 1.09; 99% CI, 1.00-1.19; aHR for 8-10 weeks, 1.10; 99% CI, 1.01-1.19; aHR for > 10 weeks, 1.12; 99% CI, 1.04-1.21; Supporting Table 5 [see online supporting information]).

DISCUSSION

The delivery of quality head and neck cancer care remains a national priority.[36] Guideline-concordant care and timeliness of care are 2 indicators of quality care.[1] Risk factors for failing to commence adjuvant therapy in a guideline-concordant, timely fashion have been described.[9] Whether failing to deliver NCCN guideline–concordant, timely PORT has an impact on survival remains unclear.[13] This study, which used a large national sample of patients from a variety of facility types treated with modern radiation techniques in the era of concurrent chemotherapy, was undertaken to better assess the relation between quality care, timely care, guideline-concordant care, and favorable patient outcomes such as survival.

Oncologic Effect of Guideline-Adherent Initiation of PORT

The rationale for the timely initiation of adjuvant radiation is that delays in treatment allow the repopulation and proliferation of residual microscopic disease and tumor clonogens[21,24,27,37] along with subsequent increases in the tumor burden and the risk of hypoxia.[13] With mathematical models, it has been estimated that persistent postoperative microscopic tumor clonogens repopulate with an estimated doubling time of 40 to 45 days.[37,38] This doubling time has been estimated to correspond to a decrease in local control of 0.09% to 0.17% for each additional day between surgery and adjuvant therapy.[25,37]

Despite the NCCN's endorsement of the preferred time to the initiation of PORT for patients with HNSCC, the evidence underlying the recommendation is conflicted with respect to its effect on locoregional recurrence and survival,[13] with some finding a benefit[14-21] and others finding no influence.[10,11,22-26] Many of these studies have been limited by a retrospective, single-institution study design and small patient numbers.[13] In this study, a 50% relative decrease in OS was found for patients who initiated adjuvant therapy more than 6 weeks after surgery, a 15% relative increased risk of death persisted in a multivariate analysis

TABLE 2. Effect of Initiating PORT Within 6 Weeks of Surgery on Overall Survival: Univariate and Multivariate Cox Proportional Hazards Models

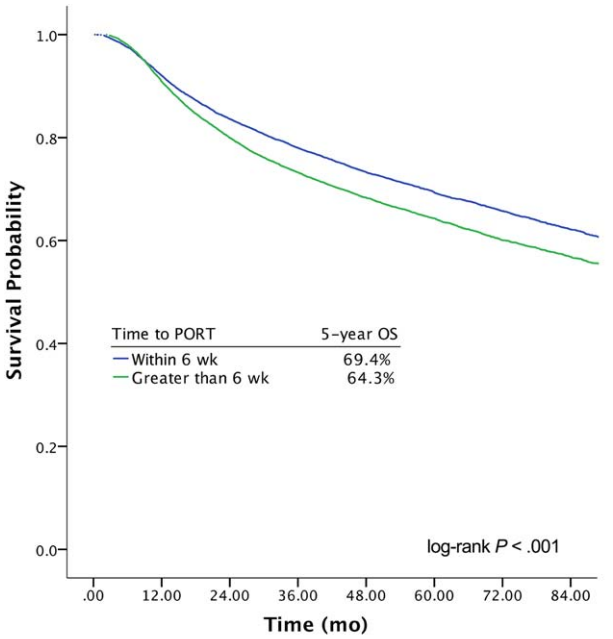
Patient Variable	Univariate Analysis: Hazard Ratio (99% CI)	Multivariate Analysis: Adjusted Hazard Ratio (99% CI)
Initiation of PORT at >6 wk	1.48 (1.41-1.55)	1.13 (1.08-1.19)
Age		
<50 y	1 (reference)	1 (reference)
50-59 y	1.23 (1.15-1.32)	1.21 (1.12-1.30)
60-69 y	1.62 (1.51-1.74)	1.37 (1.26-1.48)
≥70 y	2.67 (2.48-2.87)	1.99 (1.82-2.18)
Female sex	1.17 (1.11-1.23)	0.92 (0.87-0.97)
Race		
White	1 (reference)	1 (reference)
Black	1.44 (1.34-1.55)	1.11 (1.02-1.19)
Other	1.05 (0.93-1.19)	0.93 (0.82-1.05)
Insurance type		
Private	1 (reference)	1 (reference)
Medicare	2.39 (2.27-2.52)	1.62 (1.50-1.75)
Medicaid	2.32 (2.16-2.50)	1.47 (1.38-1.57)
Uninsured	1.79 (1.62-1.98)	1.40 (1.20-1.64)
Other	1.76 (1.50-2.05)	1.32 (1.10-1.60)
Education		
Highest quartile	1 (reference)	
2nd highest quartile	1.20 (1.12-1.28)	—[a]
2nd lowest quartile	1.37 (1.29-1.47)	
Lowest quartile	1.53 (1.42-1.65)	
Median household income		
Highest quartile	1 (reference)	1 (reference)
2nd highest quartile	1.24 (1.16-1.32)	1.11 (1.04-1.18)
2nd lowest quartile	1.36 (1.28-1.45)	1.15 (1.07-1.22)
Lowest quartile	1.62 (1.51-1.73)	1.24 (1.15-1.32)
Charlson/Deyo comorbidity score		
0	1 (reference)	1 (reference)
1	1.50 (1.42-1.59)	1.21 (1.14-1.28)
≥2	2.26 (2.07-2.46)	1.70 (1.56-1.86)
Cancer primary site		
Oral cavity	1 (reference)	1 (reference)
Oropharynx	0.33 (0.31-0.34)	0.37 (0.35-0.40)
Hypopharynx	1.22 (1.09-1.36)	1.02 (0.91-1.14)
Larynx	0.71 (0.67-0.74)	0.73 (0.69-0.78)
AJCC clinical stage grouping		
I	1 (reference)	
II	1.55 (1.41-1.70)	—[a]
III	1.41 (1.29-1.54)	
IV	1.69 (1.56-1.83)	
AJCC pathologic stage grouping		
I	1 (reference)	1 (reference)
II	1.33 (1.17-1.52)	1.27 (1.11-1.45)
III	1.29 (1.15-1.46)	1.44 (1.27-1.62)
IV	1.87 (1.68-2.08)	1.93 (1.73-2.15)
Positive surgical margins	1.03 (0.98-1.09)	—[a]
≥18 lymph nodes removed	0.97 (0.96-0.97)	—[a]
30-d hospital readmission		
None	1 (reference)	
Unplanned	1.40 (1.24-1.58)	—[a]
Planned	0.89 (0.77-1.03)	
Radiation modality		
External beam	1 (reference)	1 (reference)
IMRT	0.90 (0.86-0.94)	1.07 (1.02-1.13)
3DCT	1.38 (1.23-1.56)	1.03 (0.92-1.16)
Concurrent chemoradiation	0.95 (0.91-1.00)	1.20 (1.14-1.26)
Radiation dose		
60-66 Gy	1 (reference)	1 (reference)
<40 Gy	2.20 (2.02-2.40)	1.66 (1.51-1.82)
40-59.9 Gy	1.18 (1.11-1.25)	1.14 (1.07-1.20)
>66 Gy	0.89 (0.84-0.95)	1.15 (1.05-1.26)
Radiation treatment duration		
43-49 d	1 (reference)	1 (reference)
1-35 d	2.33 (2.15-2.53)	1.72 (1.57-1.89)
36-42 d	0.91 (0.84-0.99)	0.93 (0.86-1.01)
50-63 d	1.13 (1.07-1.19)	1.19 (1.13-1.26)
≥64 d	1.59 (1.48-0.1.71)	1.46 (1.35-1.58)
Treatment facility type		
Community	1 (reference)	
Comprehensive community	0.95 (0.87-1.03)	—[a]
Academic	1.05 (0.97-1.14)	
Integrated network	1.04 (0.93-1.15)	
Treatment at >1 CoC facility	0.98 (0.91-1.05)	—[a]
Surgery and PORT at different facilities	1.07 (1.03-1.12)	—[a]
Region of United States		
East	1 (reference)	
Central	1.05 (0.98-1.12)	—[a]
South	1.12 (1.05-1.20)	
West	0.93 (0.86-1.01)	

Abbreviations: 3DCT, 3-dimensional conformal therapy; AJCC, American Joint Committee on Cancer; CI, confidence interval; CoC, Commission on Cancer; IMRT, intensity-modulated radiation therapy; PORT, postoperative radiation therapy.
[a] Dropped out of the final multivariate model.

adjusted for numerous confounding factors, and a 20% relative increased risk of death was found in the propensity-matched subset analysis. These findings lend further support to the idea that, at least with respect to the timing of adjuvant therapy, guideline-adherent head and neck oncology care is quality care.[39-41]

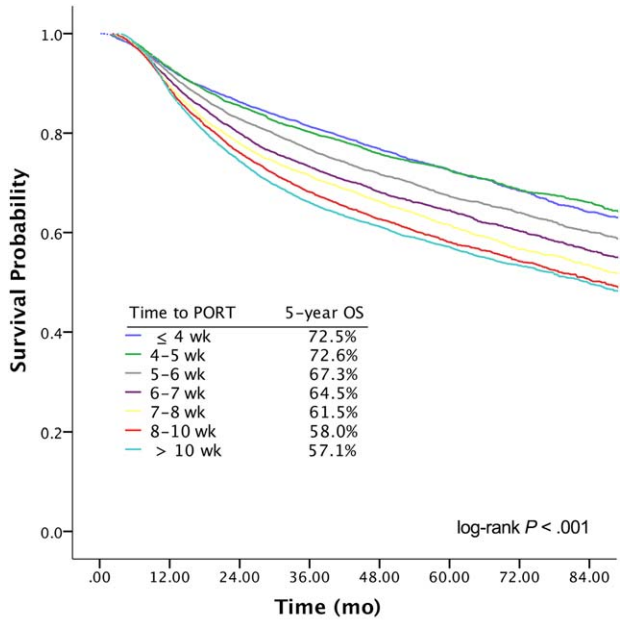
Effects of an Early Time to the Initiation of PORT on Survival

Although NCCN guidelines recommend initiating PORT within 6 weeks of surgery, it has not been well studied whether there is a benefit to starting adjuvant therapy earlier, such as within 4 or 5 weeks of surgery. Some have advocated commencing adjuvant therapy as soon as possible.[27] In the current study, there was no statistical or clinically meaningful benefit in terms of OS to starting PORT ≤4 weeks or 4 to 5 weeks after surgery in comparison with 5 to 6 weeks after surgery. This may be due to the time course and biology of tumor repopulation. Alternatively, it could be a result of a selection bias in which patients who were perceived as having more aggressive disease were expedited to start adjuvant therapy earlier after surgery, and this



	No. at Risk							
	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo
PORT at ≤6 wk	14,951	13,207	10,732	8263	6229	4481	3000	1895
PORT at >6 wk	14,951	13,151	10,292	7789	5815	4161	2732	1677

Figure 2. Kaplan-Meier estimates of OS in the propensity score–matched subset analysis (n = 29,910) demonstrating the effect of NCCN guideline–adherent initiation of PORT within 6 weeks of surgery versus non–guideline-adherent care initiating PORT more than 6 weeks postoperatively. NCCN indicates National Comprehensive Cancer Network; OS, overall survival; PORT, postoperative radiation therapy.



	No. at Risk							
	0 mo	12 mo	24 mo	36 mo	48 mo	60 mo	72 mo	84 mo
PORT at ≤4 wk	6494	5794	4863	3878	3018	2186	1487	940
PORT at 4-5 wk	5635	5019	4134	3203	2458	1792	1173	745
PORT at 5-6 wk	6333	5625	4520	3446	2541	1794	1218	768
PORT at 6-7 wk	6015	5270	4137	3080	2279	1651	1085	682
PORT at 7-8 wk	4685	4078	3107	2306	1686	1182	727	470
PORT at 8-10 wk	5515	4724	3538	2605	1910	1319	866	515
PORT at >10 wk	6614	5655	4253	3166	2366	1664	1073	640

Figure 3. Kaplan-Meier estimates of OS demonstrating the impact of increasing the time to the initiation of PORT (n = 41,291). Each PORT time interval is not inclusive of the lower bound and is inclusive of the upper bound. OS indicates overall survival; PORT, postoperative radiation therapy.

obscured the beneficial effect of an earlier initiation of PORT. It might also be that other endpoints such as locoregional recurrence are more suitable outcome measures when one is assessing the effect of the time to the initiation of adjuvant therapy. Further studies will be required to determine whether there is a benefit overall or in specific subgroups from the earlier initiation of adjuvant therapy.

Effects of Increasing Durations of Delay to the Initiation of PORT on Survival

It also remains understudied whether increasing durations of delay beyond 6 weeks after surgery are associated with correspondingly worse outcomes. In this study, all time intervals for which PORT was initiated more than 7 weeks after surgery were associated with decreased survival, but there were not clinically meaningful differences in the excess risk of death with increasing durations of delay in the multivariate analysis. Although these data do not support intentionally delaying adjuvant therapy, in cases of prolonged postoperative wound complications in which it is unsafe to start radiation sooner, they show a continued linear increase in the risk of death that comes with an increasing duration of delay.

Limitations

This study possesses important limitations. Although the NCDB data are captured by trained data extractors and extensive quality-control measures exist, coding errors and data omissions are possible, are likely not random, and may bias the results of this study. Although the type of surgery is coded within the NCDB, it is likely that some biopsies were coded as definitive surgery, and this potentially biased the results. Differentiating between coding errors and outlier data is also challenging and is another source of potential error. Because this is a retrospective database study, reasons for delays in starting PORT in a guideline-adherent fashion cannot be discerned. These might include tumor board discussions,

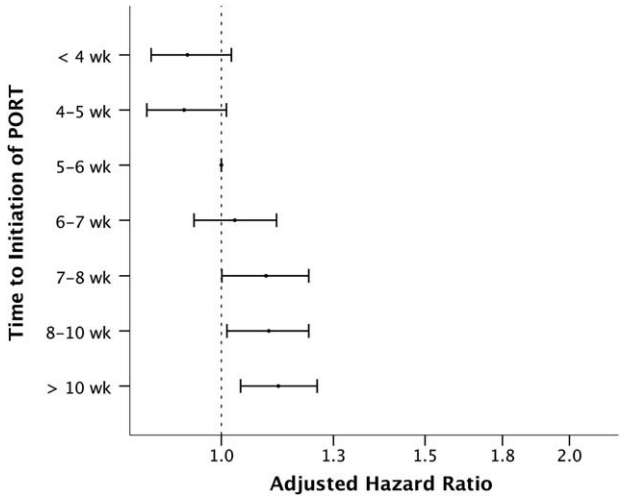


Figure 4. Effect of changing the time to the initiation of PORT on overall survival after a multivariate Cox proportional hazards analysis in comparison with starting adjuvant therapy between 5 and 6 weeks after surgery (n = 41,291). Estimated hazard ratios are shown as black circles; the horizontal lines represent 99% confidence intervals. Each PORT time interval is not inclusive of the lower bound and is inclusive of the upper bound. The analyses have been adjusted for age, race, sex, insurance, income, Charlson/Deyo comorbidity score, primary site, American Joint Committee on Cancer pathologic stage grouping, concurrent chemotherapy, radiation modality, radiation dose, and duration of radiation. PORT indicates postoperative radiation therapy.

patient-physician discussions about the risk/benefit ratio of adjuvant therapy, decision making about the need for and referral for PORT, patient preferences, indecisiveness, and the ability to access care and meet the schedule of postoperative appointments necessary for the timely initiation of PORT. PSM was used to control for treatment biases of a retrospective, observational design, and although it was successful in balancing differences between the 2 cohorts of patients, it could not control for variables not captured in the NCDB. The time to the initiation of PORT, although it is the only time-sensitive metric within current NCCN guidelines, is only one portion of timely care. This study does not evaluate delays in presentation, diagnosis, or initiation of surgery or the total treatment package time from the date of surgery to the completion of PORT, all of which also affect survival.[21,42] OS is multifactorial in nature. Although improved OS was seen with guideline-adherent initiation of PORT, it does not suggest that the timely initiation of PORT indicates improved locoregional control or disease-specific survival. The effects of the time to the initiation of PORT on rates of locoregional failure or disease-free survival are relevant outcome measures not analyzed in the study because these data are not available in the NCDB; future studies should consider these as outcome measures when they are evaluating the timeliness of PORT. Despite these limitations, there are numerous methodological strengths to the study. It captures patients of all adult ages, has a national scope and a large sample size, and analyzes treatment at different types of hospitals.

In conclusion, care not adherent to NCCN guidelines for initiating PORT within 6 weeks of surgery is associated with decreased survival. There is no OS benefit to initiating PORT earlier within the recommended 6-week timeframe. Increasing durations of delay beyond 7 weeks are associated with small, progressive survival decrements.

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The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Each author has participated sufficiently in the work to take public responsibility according to International Committee of Medical Journal Editors guidelines: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting of the article or its critical revision for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work.

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