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The impact of treatment package time on survival in surgically managed head and neck cancer in the United States

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ABSTRACT

Objectives: Delays in the initiation of postoperative radiation have been associated with worse outcomes; however, the effect of the overall treatment package time (interval from surgery through the completion of radiation) remains undefined. The purpose of this study was to determine the impact of package time on survival and to evaluate this effect among different subgroups of head and neck cancer patients.

Patients and methods: In this observational cohort study, the National Cancer Database was used to identify 35,167 patients with resected nonmetastatic head and neck cancer who underwent adjuvant radiation from 2004 to 2014. Kaplan-Meier survival estimates and multivariate Cox regression analyses were performed to determine the effect of treatment package time on overall survival.

Results: Median package time was 96 days (interquartile range, 85–112 days). After adjusting for covariates, package times of 11 weeks or less were associated with improved survival (adjusted hazard ratio (aHR), 0.90; 95% confidence interval, 0.83–0.97) compared to an interval of 12–13 weeks, whereas package times of more than 14 weeks were associated with worse survival (aHR, 1.14, 1.14, and 1.22 for 14–15, 15–17, and > 17 weeks, respectively). A significant interaction was identified between package time and disease site, nodal status, and stage. Specifically, patients with oropharyngeal tumors, advanced stage (III or IV) disease, or nodal involvement experienced more pronounced increases in mortality risk with delays in treatment time.

Conclusions: Treatment package time independently impacts survival. This effect may be strongest for patients with oropharyngeal tumors or advanced stage disease.

Introduction

Adjuvant radiation and chemotherapy confer improved locoregional control and overall survival in appropriately selected patients with head and neck squamous cell carcinoma (HNSCC) [1–3]. Accelerated repopulation of residual tumor clonogens after surgical resection and during postoperative chemoradiation delivery is well-established, and this phenomenon mandates timely completion of the total treatment package of operation plus adjuvant therapy [4–7]. Although several studies have confirmed that the prolongation of radiation therapy when used as a definitive treatment in HNSCC is associated with poor oncologic outcome [8–10], the relative importance of delays in the completion of adjuvant radiotherapy remains controversial. While several studies have shown improved outcomes with shorter treatment package time (TPT) [1,11–13], others have found no demonstrable benefit [14–16]. No formal guideline for optimal package time exists and proposed intervals in the literature range widely from 77 days to 100 days [1,11–13]. These recommendations are mostly drawn from analyses of patients treated more than 20 years ago. Whether recent advancements in adjuvant radiotherapy including intensity-modulated radiation therapy, altered fractionation, and concurrent chemotherapy have altered the impact of prolonged treatment times remains unclear. Furthermore, while it has been suggested that the effect of delayed diagnosis or initiation of treatment may differ considerably among specific groups of HNSCC patients (e.g. different tumor subsites) [17,18], the effect of prolonged TPT among subsets of HNSCC patients

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has yet to be thoroughly investigated. We sought to determine the impact of prolonged TPT on survival and whether this effect varies among certain subgroups of HNSCC patients using a large national registry.

Patients and methods

Data source

The National Cancer Database (NCDB) is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB is a nationwide, hospital-based registry with annual data collected from > 1500 CoC-accredited facilities that represent > 70% of newly diagnosed cancer cases in the United States [19]. Because the database uses publicly available information with no personal identifiers, full review by the University of California- Los Angeles Institutional Review Board was not required.

Study population

We identified patients from the NCDB from 2004 to 2014 who had nonmetastatic head and neck squamous cell carcinoma treated with curative-intent surgical resection and adjuvant radiation with or without chemotherapy. Cancer subsites included the oral cavity, oropharynx, larynx, and hypopharynx as indicated by International Classification of Diseases for Oncology (3rd edition) topography codes, as previously described [20]. Patients undergoing more limited procedures such as excisional biopsy or local destructive therapy (cryotherapy, laser excision) were excluded. Patients were also excluded for non-external beam radiation, total radiation dose to the head and neck of less than 50 Gy or more than 76 Gy, neoadjuvant chemotherapy, unknown package time, missing follow-up, definitive surgery more than 180 days after the diagnosis, or duration of radiotherapy of less than 30 days or more than 90 days (Fig. 1). For each patient, the total treatment package time was calculated as the number of days from the date of surgery through the end of radiotherapy. After examining the distribution of TPT in our cohort, we excluded patients with package times > 210 days (95th percentile), as this was deemed to be non-representative of a unified course of surgery and adjuvant therapy. We also excluded patients with TPT < 50 days, which was considered to be the minimum time to complete a definitive treatment regimen [21].

Covariates

Patient clinical and demographic variables included age, sex, race, and Charlson/Deyo comorbidity index. Median household income and percent of adults without a high school education by zip code of residence are estimated by the NCDB based on census data and categorized by quartile of the US population. Primary health insurance coverage was grouped as Medicaid, Medicare, other (private care/managed care/governmental insurance), none, or unknown. Oncologic characteristics included tumor site, lymph node involvement, extracapsular extension, and American Joint Committee on Cancer (AJCC) pathologic stage. Treatment variables included surgical margins, 30-day unplanned hospital readmission, time from diagnosis to surgery, treatment package time, radiation modality, radiation dose, administration of concurrent chemotherapy, treatment facility type, geographic location of facility, and receipt of surgery and radiation at the same facility. Facility types were defined as academic, Commission on Cancer designated Comprehensive Community Cancer Program (CCCP), community, or other. The time from diagnosis to surgery was categorized with a 68-day cutoff, a threshold that has previously been correlated with outcomes in NCDB data [17].

Statistical analysis

Package time was initially modeled as a categorical variable with three groups (≤12 weeks, 12–14 weeks, and > 14 weeks), with these

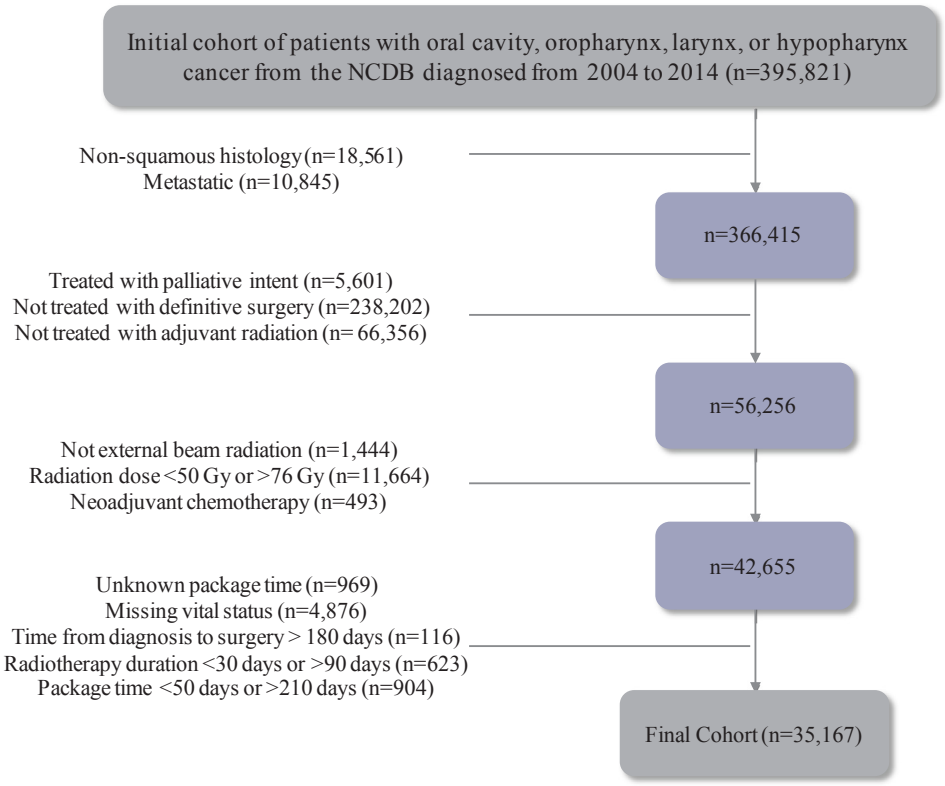

Fig. 1. Diagram of patients included in the analytic cohort. NCDB, National Cancer Database.

prespecified thresholds based on prior studies proposing the total package should be delivered within 12–14 weeks [11–13]. Differences between covariates by TPT category were tested using χ^2 tests. The primary endpoint was overall survival (OS) from the date of diagnosis to death from any cause and was estimated using the Kaplan-Meier method with comparisons made using log-rank tests. Univariate Cox proportional hazard regression analysis was performed to identify factors associated with OS. Variables significantly associated with OS ($P < 0.05$) in the univariate model were included in Cox multivariate regression model to identify independent predictors of OS. We explored the interactions between TPT and site of disease, stage, lymph node involvement, extracapsular extension (ECE), surgical margins, and adjuvant chemotherapy use [22]. When testing the interaction with lymph node involvement and ECE, we only included the subset of patients with stage III or IV disease.

To determine the relationship between TPT and survival at a more granular level, TPT was further stratified into a categorical variable with 7 groups: ≤11, 11–12, 12–13, 13–14, 14–15, 15–17, and > 17 weeks (intervals are inclusive of the upper bound and not inclusive of the lower bound). The overall package time was analyzed as a categorical variable instead of a continuous variable because of the easier clinical interpretation and application of hazard ratios [20]. The Kaplan-Meier method was used to estimate survival, and multivariate Cox proportional hazard regressions were performed to assess the effect of TPT on OS after adjusting for covariates. Statistical significance was set at $P < 0.05$, and all tests were two-sided. Analyses were performed using Stata 14 (StataCorp, College Station, TX).

Results

Baseline population characteristics

In all, 35,167 patients with nonmetastatic squamous cell carcinoma of the head and neck undergoing definitive surgical resection and adjuvant radiotherapy from 2004 to 2014 were included in the study. The characteristics of the study population are shown in Table 1. The median age at diagnosis was 59 years (52–66 years). The majority of patients were male (73.3%) and white (88.0%). The median treatment package time was 96 days (IQR, 85–112 days) and mean was 101 days (standard deviation (SD), 24 days). Package time was further divided into the time from surgery to the initiation of radiation and the duration of radiotherapy (Fig. 2). The median and mean number of days from surgery to initiation of radiation were 48 days (IQR, 38–62 days) and 52 days (SD, 22 days), respectively, while the median and mean number of days elapsed during radiotherapy was 47 days (IQR, 45–52 days) and 49 days (SD, 8 days), respectively.

We compared total package times by patient and treatment characteristics (Table 1). Differences in package times were significantly associated with all variables included in our analysis. To highlight a few of these differences, patients with longer package times were more likely to have been black and reside in lower education and income areas, and these patients were more likely to have non-private insurance, more comorbidities, non-oropharyngeal tumors, stage IV disease, and to have received surgery and radiation at different facilities. In addition, the proportion of patients with package times more than 14 weeks increased over the study period.

Treatment package time and survival

The median follow-up time for surviving patients was 52.4 months (interquartile range, 31.5–80.7 months). Of 8029 patients with a TPT ≤ 12 weeks, 2190 (27.3%) had died by the end of the study, compared to 3634 of 11,084 (32.8%) patients with a TPT of 12–14 weeks, and 6592 of 16,054 (41.0%) patients with a TPT more than 14 weeks. The median overall survival estimates were 11.8 years (95% confidence interval (CI), 11.3–12.1 years), 9.9 years (95% CI, 9.5–10.5 years), and 7.4 years (95% CI, 7.1–7.7 years), for total package times of ≤12 weeks, 12–14 weeks, and > 14 weeks, respectively (log-rank $P < 0.001$; Fig. 3).

The results of the univariate and multivariate Cox regression are shown in Table 2. After adjusting for covariates, compared to a TPT of 12–14 weeks, TPT of 12 weeks or less was associated with significantly decreased risk of mortality (adjusted hazard ratio (aHR), 0.93; 95% CI, 0.89–0.98; $P = 0.013$), while TPT more than 14 weeks was associated with increased risk of mortality (aHR, 1.17; 95% CI, 1.12–1.22; $P < 0.001$). When analyzed as a continuous variable, each incremental week of total package time was associated with an average 3% increase in risk of death (aHR 1.03; 95% CI, 1.02–1.03; $P < 0.001$). Other factors significantly associated with worse OS included residing in a low income area, advanced comorbidity, advanced stage, positive margin status, ECE, lymph node involvement, and radiation doses higher or lower than 60–66 Gy. Having Medicaid (aHR, 1.57; 95% CI, 1.48–1.67) or Medicare (aHR, 1.39; 95% CI, 1.33–1.47) insurance was associated with worse OS compared to having private/managed care/other government insurance. Compared to patients treated at academic centers, those treated at CCCPs also had inferior outcomes (aHR, 1.06; 95% CI, 1.02–1.11).

To more closely examine the impact of particular treatment package time intervals, the survival analysis was performed with TPT further stratified into a categorical variable with 7 groups. Kaplan-Meier estimates of OS with different package times are shown in Fig. 4A. On multivariate analysis, in comparison to a TPT of 12–13 weeks, overall package times of 11 weeks or less were associated with significantly reduced risk of mortality (aHR, 0.90; 95% CI, 0.83–0.97; $P = 0.013$; Fig. 4B). Conversely, increasing total package times beyond 14 weeks were associated with significantly greater risk of mortality in the multivariate model (14–15 weeks: aHR, 1.14; 95% CI, 1.07–1.22; 15–17 weeks: aHR, 1.14; 95% CI, 1.07–1.22; > 17 weeks: aHR, 1.22; 95% CI, 1.15–1.30).

Interaction effects of package time and other covariates

Subgroup effects of interactions between TPT and tumor subsite, disease stage, nodal involvement, margin status, extracapsular extension, and adjuvant chemotherapy use were tested with multivariate Cox regression. There was a significant interaction of TPT with tumor subsite, nodal involvement, and disease stage, but not margin status, ECE, or adjuvant chemotherapy use (Fig. 5). Compared to total package times of 12–14 weeks, those of 12 weeks or less were associated with decreased risk of mortality in oropharyngeal tumors (HR, 0.90; 95% CI, 0.82–0.99), but did not demonstrate significant survival benefit in oral cavity, laryngeal, or hypopharyngeal disease sites (Fig. 5A). Package times of more than 14 weeks were significantly associated with worse OS for oral cavity, laryngeal, and oropharyngeal tumors, and this relationship was also strongest for oropharyngeal tumors. For patients with hypopharyngeal tumors, there was a trend towards worse OS with package times more than 14 weeks that did not quite reach statistical significance. The effect of TPT on mortality risk was more pronounced in advanced stage (III or IV) disease compared to early stage (I or II) disease (Fig. 5B). For patients with advanced disease, compared to a 12- to 14-week interval, TPT of 12 weeks or less was associated with improved OS (aHR, 0.88; 95% CI, 0.82–0.95), and TPT more than 14 weeks conferred worse survival (aHR, 1.19; 95% CI, 1.13–1.25). In contrast, for patients with early stage cancer, neither package times of 12 weeks or less nor those greater than 14 weeks led to significantly different risk of mortality relative to a 12- to 14-week interval. Among the subset of patients with stage III or IV disease, those with nodal metastases had improved survival with TPT of 12 weeks of less compared to a 12- to 14-week interval (aHR, 0.90; 95% CI, 0.82–0.98), whereas this benefit was not observed in those without nodal metastases (Fig. 5C).

Table 1
Baseline Characteristics of Patients According to Treatment Package Time.

Characteristic	No. (%)				P-value
	Total (n = 35 167)	TPT ≤12 wk (n = 8 029)	TPT of 12–14 wk (n = 11 084)	TPT > 14 wk (n = 16 054)	
Sex					< 0.001
Male	25 782 (73)	6 138 (76)	8 153 (74)	11 491 (72)	
Female	9 385 (27)	1 891 (24)	2 931 (26)	4 563 (28)	
Age, y					< 0.001
≤50	7 502 (21)	1 891 (24)	2 393 (22)	3 218 (20)	
51–60	12 401 (35)	2 923 (36)	3 894 (35)	5 584 (35)	
61–70	9 759 (28)	2 142 (27)	3 099 (28)	4 518 (28)	
≥71	5 505 (16)	1 073 (13)	1 698 (15)	2 734 (17)	
Race					< 0.001
White	30 939 (88)	7 337 (91)	9 864 (89)	13 738 (86)	
Black	2 929 (8)	430 (5)	808 (8)	1 691 (10)	
Other	1 299 (4)	262 (3)	412 (4)	625 (4)	
Education[a]					< 0.001
≥21%	5 671 (16)	995 (12)	1 638 (15)	3 038 (19)	
13–20.9%	9 219 (26)	1 972 (25)	2 813 (25)	4 434 (28)	
7–12.9%	11 680 (33)	2 627 (33)	3 821 (35)	5 232 (33)	
< 7%	8 292 (24)	2 372 (30)	2 716 (25)	3 204 (20)	
Unknown	305 (1)	63 (1)	96 (1)	146 (1)	
Income, $[b]					< 0.001
< 38 000	6 151 (17)	1 124 (14)	1 829 (17)	3 198 (20)	
38 000–47 999	8 480 (24)	1 803 (22)	2 641 (24)	4 036 (25)	
48 000–62 999	9 508 (27)	2 305 (29)	2 987 (27)	4 216 (26)	
≥63 000	10 702 (30)	2 724 (34)	3 529 (32)	4 449 (28)	
Unknown	326 (1)	73 (1)	98 (1)	155 (1)	
Insurance					< 0.001
Medicare	10 820 (31)	2 140 (27)	3 326 (30)	5 354 (33)	
Medicaid	3 502 (10)	458 (6)	953 (9)	2 091 (13)	
Private/managed care/other government	18 588 (53)	5 009 (62)	6 161 (56)	7 418 (46)	
None	1 789 (5)	303 (4)	520 (5)	966 (6)	
Unknown	468 (1)	119 (1)	124 (1)	225 (1)	
Charlson/Deyo score					< 0.001
0	27 798 (79)	6 565 (82)	8 852 (80)	12 381 (77)	
1	5 933 (17)	1 199 (15)	1 802 (16)	2 932 (18)	
≥2	1 436 (4)	265 (3)	430 (4)	741 (5)	
Disease site					< 0.001
Oral cavity	14 186 (40)	2 302 (29)	4 344 (39)	7 540 (47)	
Oropharynx	15 141 (43)	4 656 (58)	4 975 (45)	5 510 (34)	
Larynx	5 013 (14)	945 (12)	1 522 (14)	2 546 (16)	
Hypopharynx	827 (2)	126 (2)	243 (2)	458 (3)	
AJCC pathologic stage					< 0.001
I	1 811 (5)	480 (6)	555 (5)	776 (5)	
II	2 683 (8)	607 (8)	848 (8)	1 228 (8)	
III	5 475 (16)	1 289 (16)	1 759 (16)	2 427 (15)	
IV	19 018 (54)	3 857 (48)	6 122 (55)	9 039 (56)	
Unknown	6 180 (18)	1 796 (22)	1 800 (16)	2 584 (16)	
Lymph node involvement					< 0.001
No	11 329 (32)	2 294 (29)	3 538 (32)	5 497 (34)	
Yes	16 848 (48)	4 223 (53)	5 384 (49)	7 241 (45)	
Unknown	6 990 (20)	1 512 (19)	2 162 (20)	3 316 (21)	
Extracapsular extension					< 0.001
No	27 022 (77)	6 276 (78)	8 675 (78)	12 071 (75)	
Yes	2 827 (8)	520 (6)	861 (8)	1 446 (9)	
Unknown	5 318 (15)	1 233 (15)	1 548 (14)	2 537 (15.8)	
Margin status					< 0.001
Negative	24 398 (69)	5 325 (66)	7 743 (70)	11 330 (71)	
Positive	8 628 (25)	2 058 (26)	2 702 (24)	3 868 (24)	
Unknown	2 141 (6)	646 (8)	639 (6)	856 (5)	
Modality of external beam radiation					< 0.001
3D-conformal	905 (3)	228 (3)	244 (2)	433 (3)	
IMRT	20 816 (59)	4 775 (59)	6 700 (60)	9 341 (58)	
Unspecified	13 446 (38)	3 026 (38)	4 140 (37)	6 280 (39)	
Radiation dose					< 0.001
50.00–59.99	9 718 (28)	2 145 (27)	2 938 (27)	4 635 (29)	
60.00–65.99	13 686 (39)	3 104 (39)	4 547 (41)	6 035 (38)	
66.00–69.99	7 279 (21)	1 489 (19)	2 305 (21)	3 485 (22)	
70.00–76.00	4 484 (13)	1 291 (16)	1 294 (12)	1 899 (12)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	No. (%)				P-value
	Total (n = 35 167)	TPT ≤12 wk (n = 8 029)	TPT of 12–14 wk (n = 11 084)	TPT > 14 wk (n = 16 054)	
Adjuvant chemotherapy					< 0.001
No	16 413 (47)	3 539 (44)	5 204 (47)	7 670 (48)	
Yes	18 193 (52)	4 369 (54)	5 718 (52)	8 106 (51)	
Unknown	561 (2)	121 (2)	162 (1)	278 (2)	
Facility					< 0.001
Academic	17 245 (49)	3 589 (45)	5 535 (50)	8 121 (51)	
Comprehensive community	10 970 (31)	2 802 (35)	3 388 (31)	4 780 (30)	
Community	2 165 (6)	484 (6)	660 (6)	1 021 (6)	
Other	4 787 (14)	1 154 (14)	1 501 (14)	2 132 (13)	
Surgery and radiation at same facility					< 0.001
No	15 919 (45)	3 097 (39)	4 838 (44)	7 984 (50)	
Yes	18 242 (52)	4 717 (59)	5 947 (54)	7 578 (47)	
Unknown	1 006 (3)	215 (3)	299 (3)	492 (3)	
Time from diagnosis to surgery, d					< 0.001
< 68	32 712 (93)	7 675 (96)	10 354 (93)	14 683 (91)	
≥68	2 455 (7)	354 (4)	730 (7)	1 371 (9)	
30-day unplanned readmission					< 0.001
No	32 499 (92)	7 547 (94)	10 312 (93)	14 640 (91)	
Yes	1 094 (3)	184 (2)	335 (3)	575 (4)	
Unknown	1 574 (4)	298 (4)	437 (4)	839 (5)	
Year of diagnosis					< 0.001
2004–2006	6 583 (19)	1 495 (19)	2 059 (19)	3 029 (19)	
2007–2010	11 702 (33)	2 638 (33)	3 491 (32)	5 573 (35)	
2011–2014	16 882 (48)	3 896 (49)	5 534 (50)	7 452 (46)	
Region of United States					< 0.001
East	6 996 (20)	1 249 (16)	2 210 (20)	3 537 (22)	
South	11 473 (33)	2 482 (31)	3 540 (32)	5 451 (34)	
Central	10 206 (29)	2 713 (34)	3 356 (30)	4 137 (26)	
West	5 248 (15)	1 270 (16)	1 575 (14)	2 403 (15)	
Unknown	1 244 (4)	315 (4)	403 (4)	526 (3)	

Abbreviations: TPT, treatment package time; 3-D, 3-dimensional; IMRT, intensity modulated radiation therapy.
[a] Education indicates the percent of people with no high school degree in the patient's zip code of residence.
[b] Income indicates the median household income in the patient's zip code of residence.

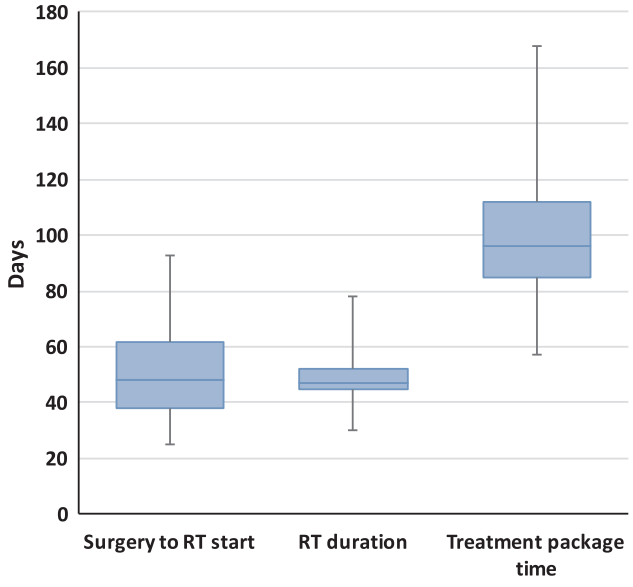

Fig. 2. Distributions of total package time, time between surgery and radiation, and duration of radiotherapy for the overall cohort. The central line represents the median. The shaded box represents the interquartile range (IQR). Brackets represent the highest and lowest values within 1.5× of the interquartile range (IQR). Outliers beyond the IQR are omitted for clarity of presentation. RT, radiotherapy.

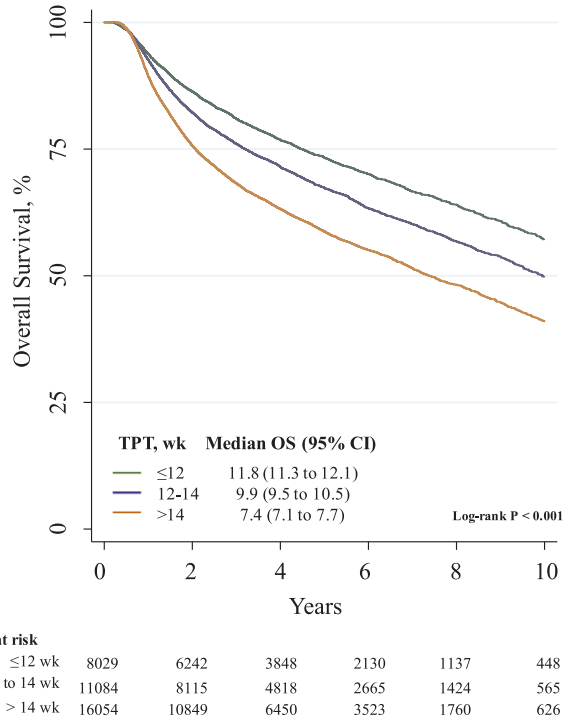

Fig. 3. Kaplan-Meier estimates of OS according to total treatment package time modeled as a categorical variable with 3 groups.

Table 2
Multivariate Cox Regression for All-Cause Mortality.

Variable	Hazard Ratio (95% CI)	P-value
Treatment package time		
≤12 wk	0.93 (0.88–0.99)	0.01
12–14 wk	1 (Reference)	
> 14 wk	1.17 (1.12–1.22)	< 0.001
Sex		
Male	1 (Reference)	
Female	0.89 (0.86–93)	< 0.001
Age, y		
≤50	1 (Reference)	
51–60	1.28 (1.21–1.36)	< 0.001
61–70	1.45 (1.36–1.55)	< 0.001
≥71	2.05 (1.91–2.22)	< 0.001
Race		
White	1 (Reference)	
Black	1.04 (0.98–1.11)	0.20
Other	0.92 (0.83–1.02)	0.11
Education[a]		
≥21%	1 (Reference)	
13–20.9%	1.03 (0.97–1.09)	0.30
7–12.9%	1.03 (0.97–1.10)	0.28
< 7%	1.02 (0.95–1.10)	0.53
Unknown	1.92 (0.84–4.33)	0.12
Income, $[b]		
< 38 000	1 (Reference)	
38 000–47 999	0.95 (0.90–1.00)	0.08
48 000–62 999	0.90 (0.85–0.96)	0.001
≥63 000	0.84 (0.78–0.90)	< 0.001
Unknown	0.89 (0.40–2.00)	0.78
Insurance		
Medicare	1.39 (1.33–1.47)	< 0.001
Medicaid	1.57 (1.48–1.67)	< 0.001
Private/managed care/other government	1 (Reference)	
None	1.30 (1.20–1.41)	< 0.001
Unknown	1.13 (0.97–1.32)	0.13
Charlson/Deyo score		
0	1 (Reference)	
1	1.17 (1.12–1.22)	< 0.001
≥2	1.55 (1.44–1.67)	< 0.001
Disease site		
Oral cavity	1 (Reference)	
Oropharynx	0.36 (0.35–0.38)	< 0.001
Larynx	0.86 (0.82–0.90)	< 0.001
Hypopharynx	1.01 (0.92–1.10)	0.88
AJCC pathologic stage		
I	1 (Reference)	
II	1.13 (1.01–1.26)	0.04
III	1.24 (1.12–1.37)	< 0.001
IV	1.58 (1.43–1.74)	< 0.001
Unknown	1.31 (1.19–1.46)	< 0.001
Lymph node involvement		
No	1 (Reference)	
Yes	1.15 (1.10–1.20)	< 0.001
Unknown	1.02 (0.97–1.08)	0.43
Extracapsular extension		
No	1 (Reference)	
Yes	1.32 (1.24–1.40)	< 0.001
Unknown	0.90 (0.85–0.95)	< 0.001
Margin status		
Negative	1 (Reference)	
Positive	1.25 (1.20–1.30)	< 0.001
Unknown	1.08 (0.99–1.18)	0.07
Modality of external beam radiation		
3D-conformal	1 (Reference)	
IMRT	0.93 (0.84–1.03)	0.16
Unspecified	0.95 (0.95–1.05)	0.31
Radiation dose		
50.00–59.99	1.08 (1.03–1.13)	0.001
60.00–65.99	1 (Reference)	
66.00–69.99	1.09 (1.04–1.14)	0.001
70.00–76.00	1.15 (1.08–1.23)	< 0.001
Adjuvant chemotherapy		
No	1 (Reference)	
Yes	1.07 (1.02–1.11)	0.002
Unknown	0.76 (0.66–0.88)	< 0.001
Facility		
Academic	1 (Reference)	
Comprehensive community	1.06 (1.02–1.11)	0.004
Community	1.07 (0.99–1.16)	0.07
Other	0.98 (0.92–1.04)	0.53
Surgery and radiation at same facility		
No	1 (Reference)	
Yes	0.98 (0.94–1.02)	0.26
Unknown	1.02 (0.91–1.14)	0.71
Time from diagnosis to surgery, d		
< 68	1 (Reference)	
≥68	0.98 (0.91–1.04)	0.45
30-day unplanned readmission		
No	1 (Reference)	
Yes	1.02 (0.93–1.12)	0.73
Unknown	1.06 (0.98–1.15)	0.15
Year of diagnosis		
2004–2006	1 (Reference)	
2007–2010	0.91 (0.87–0.96)	< 0.001
2011–2014	0.87 (0.82–0.92)	< 0.001
Region of United States		
East	1 (Reference)	
South	1.06 (1.01–1.12)	0.03
Central	1.04 (0.98–1.09)	0.18
West	1.01 (0.95–1.07)	0.82
Unknown	0.97 (0.84–1.11)	0.65

Abbreviations: CI, confidence interval; 3-D, 3-dimensional; IMRT, intensity modulated radiation therapy.

[a] Education indicates the percent of people with no high school degree in the patient's zip code of residence.

[b] Income indicates the median household income in the patient's zip code of residence.

Discussion

The relationship between treatment package time and outcomes in patients with HNSCC remains a subject of debate, especially with regard to the optimal interval for treatment delivery. Early studies by Parsons et al. [11] and Rosenthal et al. [12] proposed that the total package should not exceed 100 days (14 weeks), after observing inferior locoregional control (5% [11] and 13% [12] absolute decrease) and 2-year survival (8% [12] absolute decrease) in patients with treatment times exceeding this threshold. A multi-institutional randomized trial suggested even shorter intervals may be beneficial; five-year overall survival for patients completing treatment in < 11 weeks was 48% versus 27% for 11–13 weeks, and 27% for package times > 13 weeks ($P = 0.03$) [1]. A recent single-institution study in Germany by Tribius et al. used recursive partitioning analysis to identify an optimal overall package time of 87 days (12 weeks) [13]. Conversely, other studies have not shown a demonstrable benefit of shorter TPT regardless of threshold analyzed [14–16].

The present study supports the value of prolonged TPT as an independent predictor of poor outcomes. We demonstrate that even small increases in TPT correlate with inferior overall survival after controlling for age, disease severity, and patient comorbidities, with each additional week conferring a 3% increased risk of mortality. Additionally, we identify TPT of more than 14 weeks as the threshold most consistently associated with poor outcome. Of concern, the median TPT in

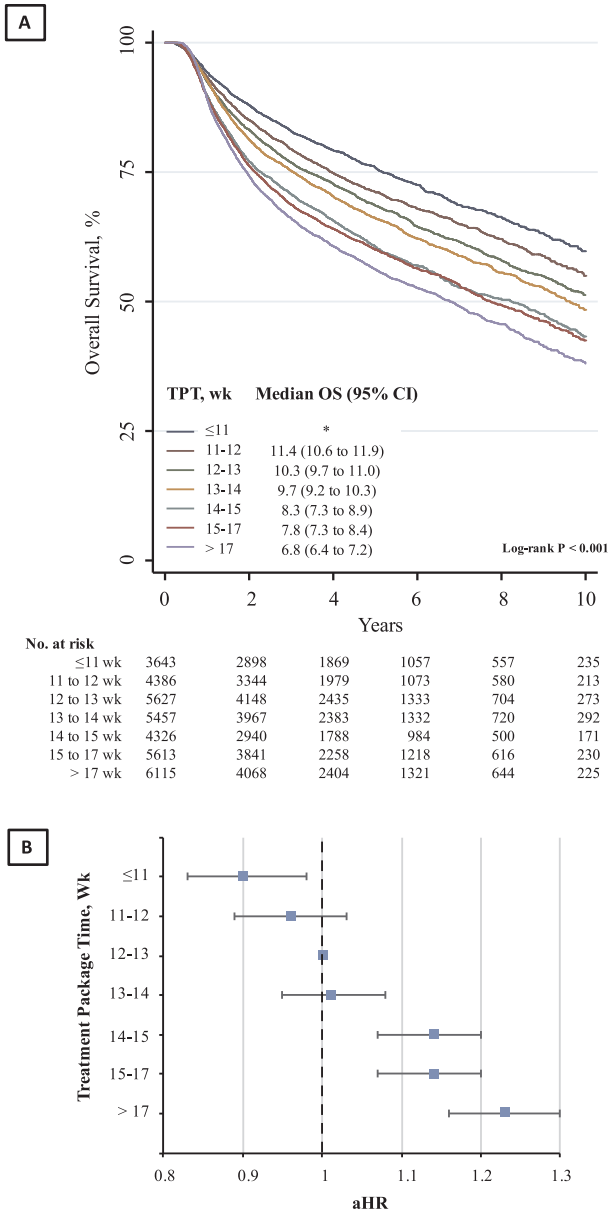

Fig. 4. (A) Kaplan-Meier estimates of OS according to total treatment package time modeled as a categorical variable with 7 groups. For TPT of 11 weeks or less, median OS exceeded the length of the follow-up period (12 years) and therefore could not be calculated. (B) Adjusted hazard ratio for mortality according to total treatment package time modeled as a categorical variable with 7 groups, with an interval of 12–13 weeks as the reference. Each TPT interval is inclusive of the upper bound but not inclusive of the lower bound. TPT, treatment package time; OS, overall survival; CI, confidence interval, aHR, adjusted hazard ratio.

our cohort was 13 weeks and 5 days, indicating that nearly half of patients are experiencing treatment times above this threshold. In our study, the effect of TPT also varied by disease site, nodal involvement, and stage, as patients with oropharyngeal tumors, advanced stage disease, and nodal metastases had more pronounced survival benefit with timely treatment delivery.

Patients in our study with a longer package time were more likely to be black and have markers of lower socioeconomic status (SES) including Medicaid or uninsured status and residence in areas with lower education and income levels. This supports prior studies demonstrating that patients of lower SES may experience increased mortality risk related to delays in time from first symptoms to initial consultation [23,24], diagnosis to surgery [25,26], and surgery to initiation of postoperative radiation [20,27]. In a cohort of patients with salivary cancer from the National Cancer Database, Morse et al. found that Medicaid insurance was, in fact, the strongest predictor of delayed overall package time after adjusting for tumor characteristics and patient comorbidities, and one of the most important predictors of overall survival [16]. Causes of delayed treatment in lower SES patients may be attributed to decreased access to care, poor health literacy, lack of social support, or transportation-related barriers [28,29]. Treatment delays in this population may exacerbate existing disparities given the tendency for lower SES patients to present with advanced stage disease, for which prompt treatment is imperative before tumors become formally unresectable or develop distant metastases [26,30].

We found significant interactions between TPT and tumor site, disease stage, and nodal involvement. Specifically, increasing package time was independently associated with decreased survival in patients with advanced stage (III and IV) tumors but not in those with early stage (I and II) tumors. Furthermore, when evaluating only patients with stage III or IV disease, the survival benefit of decreasing TPT below 12 weeks was significantly stronger in those with lymph node involvement. Some prior single-center studies have suggested that the detrimental effect of prolonged treatment time may be worse in the presence of high-risk pathologic features or advanced stage [11,12]. However, a meta-analysis of randomized controlled trials found no interaction between accelerated delivery of radiotherapy and disease stage with respect to overall survival [31]. These studies included patients treated from 1964 to 1999 which predates widespread adoption of concurrent chemotherapy and, to our knowledge, no contemporary, national database study comparing the effects of TPT across particular subgroups of HNSCC patients has previously been performed. Theoretically, larger or more aggressive tumors would be expected to have larger residual deposits of surviving tumor clonogens, resulting in increased repopulation during delays in TPT and more challenging local control. Our data highlight the distinct impact of total treatment time for patients with advanced disease, and suggest that nodal metastases may be a high-risk feature of particular importance when considering the effect of overall package time.

In our cohort, there was a significant interaction of TPT and tumor site, with package times of 12 weeks or less associated with improved OS in oropharynx tumors, but not in oral cavity, larynx, or hypopharynx tumors. Our results are consistent with prior studies showing that oropharyngeal cancers have a more pronounced response to delays in time from first symptoms to diagnosis [18], diagnosis to treatment [17], and surgery to initiation of adjuvant radiation [27]. Patients with oropharynx tumors have been shown to have 4–8 times the risk of presentation at advanced stage than those with larynx or oral cavity tumors, which may explain some of the benefit of expedited treatment given the interaction between TPT and stage we demonstrate in this study [23]. We also cannot rule out that oropharyngeal cancer patients with shorter TPT had more favorable tumor biology. Patients with human papillomavirus (HPV)-positive oropharyngeal tumors treated with surgery and adjuvant radiotherapy have been shown to have better overall survival than those with HPV-negative disease [32]. Several patient factors associated with shorter package time in our cohort such as white race, higher household income, and fewer comorbid illnesses are also known to be associated with a higher proportion of HPV-positive oropharyngeal cancer [33]. Furthermore, some patients with HPV-positive tumors may have been selected for treatment de-escalation in the form of reduced total radiation dose, potentially leading to shorter RTD. Thus, the interaction we observe may be partially explained by a tendency for patients with lower risk, HPV-positive tumors to also have more timely treatment delivery. Whether the effect of delayed package time differs between HPV-positive and -negative tumors has yet to be defined and warrants further exploration.

There are several potential solutions to these challenges. Increased

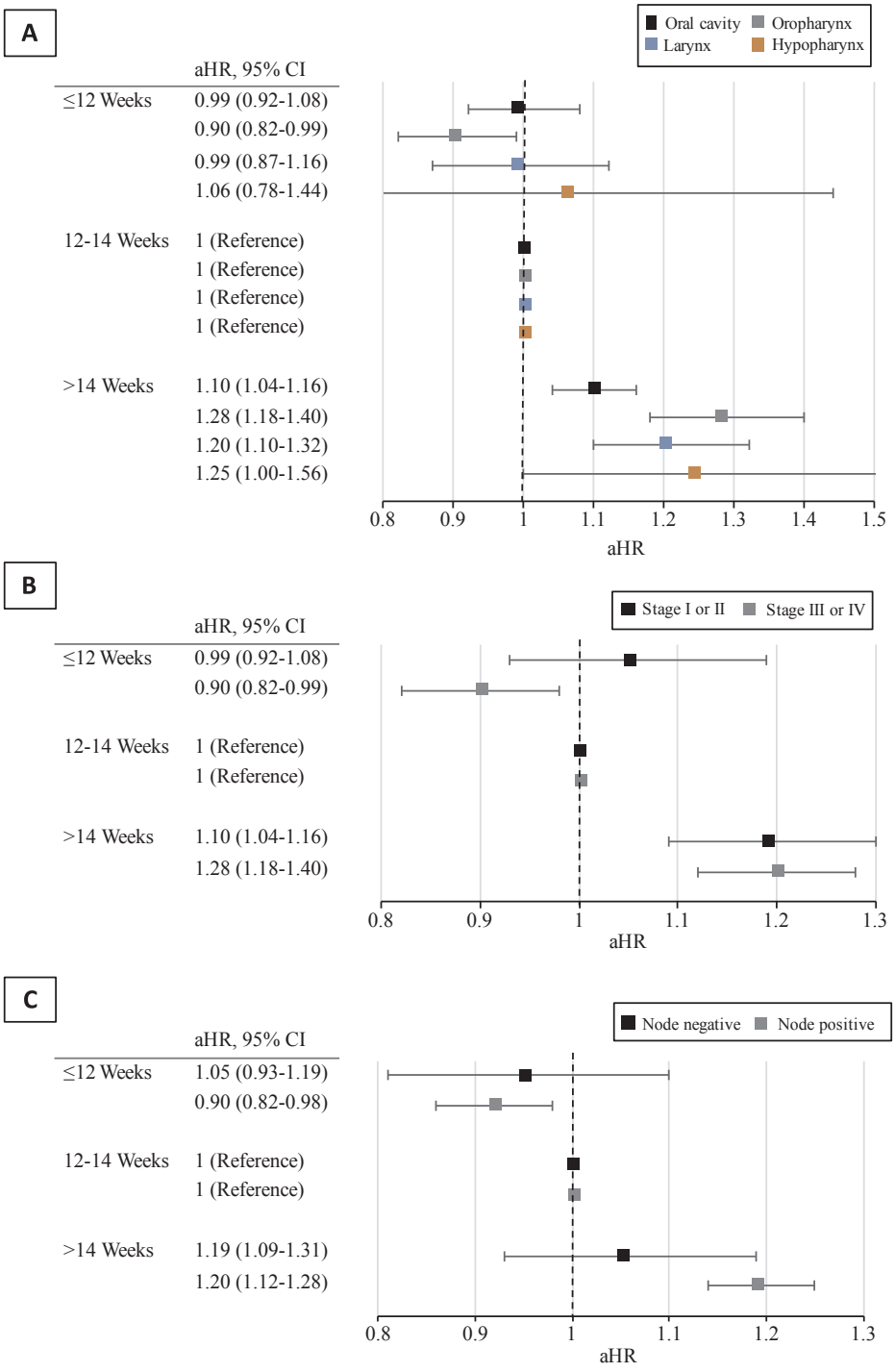

Fig. 5. Adjusted hazard ratio for mortality according to package time of ≤12 weeks or > 14 weeks compared to a package time of 12–14 weeks varied by (A) disease site, (B) disease stage, categorized as advanced (stage III or IV) and early (I or II) stage, and (C) lymph node involvement. The analysis of the subgroup effect of package time on lymph node involvement was restricted to patients with stage III or IV disease. aHR, adjusted hazard ratio; CI, confidence interval.

vertical integration of cancer care at large healthcare organizations may streamline multidisciplinary evaluations and reduce the delays related to care transitions. Accelerated fractionation schedules to compensate for unplanned interruptions in care are potentially beneficial, but may add some practical pressures to radiation therapy departments (e.g. multiple treatments for a patient in a single day) [31,34,35]. Our study takes initial steps to identifying patients that may benefit most from expedited care, potentially guiding the optimal allocation of temporal and financial resources when limited. Unplanned treatment breaks may result from acute or late toxicity to adjuvant chemoradiation [36,37]. These might be prevented or identified earlier through more frequent clinic visits during therapy, optimization of nutritional status prior to adjuvant therapy, and aggressive management of symptoms (e.g. providing supportive medications to improve odynophagia or severe skin reaction as early as possible), which may in turn improve patient outcomes [38]. Finally, patient navigation programs with a focus on addressing social barriers to care have been beneficial in the care coordination of patients with complex medical conditions, including head and neck cancer, and expansion of these programs would likely be helpful for this vulnerable population [39,40].

The NCDB database is a valuable tool that facilitated our analysis of a large patient cohort; however, as with any large registry, there are important associated limitations including those related to coding errors and missing information. Important cancer-specific outcomes such as locoregional recurrence, disease-specific survival, and toxic effects were not available for evaluation. Furthermore, although the analysis adjusted for numerous potential confounders, there are some unmeasured factors not captured in the database that may bias our findings. For example, HPV status was not available for most patients in the dataset. However, to address this, we did perform subgroup analysis by site of disease, allowing direct comparison of the effect of package time in oropharyngeal tumors relative to other subsites and confirming a trend towards worse survival with prolonged package time in all subsites. Finally, the NCDB only includes data from Commission on Cancer-accredited institutions, and therefore our findings may not be reflective of practice patterns at other institutions, such as low-volume, community facilities, that do not report to the database.

Conclusion

In conclusion, through the use of a large national tumor registry, this study demonstrated that prolonged treatment package times were independently associated with inferior overall survival. This effect was most pronounced for patients with oropharyngeal tumors and advanced stage disease. A multitude of factors were associated with treatment delay, including several markers of lower socioeconomic status. Our results highlight the importance of developing initiatives aimed at reducing unnecessary treatment interruptions and streamlining multidisciplinary care, and also identify particular patient populations that may benefit most from these interventions.

Conflict of interest statement

None declared.

Financial disclosers

None.

Status

New submission. This work has not been previously published in any language anywhere and is not under simultaneous consideration or in press by another journal.

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