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Association of Treatment Delays With Survival for Patients With Head and Neck Cancer:

A Systematic Review

Evan M. Graboyes, MD, **Anvesh R. Kompelli, BA**, **David M. Neskey, MD, MSCR**, **Emily Brennan, MLIS**, **Shaun Nguyen, MD, MA**, **Katherine R. Sterba, PhD, MPH**, **Graham W. Warren, MD, PhD**, **Chanita Hughes-Halbert, PhD**, **Brian Nussenbaum, MD, MHCM**, **Terry A. Day, MD**

Department of Otolaryngology–Head and Neck Surgery, Medical University of South Carolina, Charleston (Graboyes, Kompelli, Neskey, Brennan, Nguyen, Day); Hollings Cancer Center, Medical University of South Carolina, Charleston (Graboyes, Neskey, Sterba, Warren, Hughes-Halbert); Department of Cell and Molecular Pharmacology, Medical University of South Carolina, Charleston (Neskey, Warren); Department of Public Health Sciences, Medical University of South Carolina, Charleston (Sterba); Department of Radiation Oncology, Medical University of South Carolina, Charleston (Warren); Department of Psychiatry, Medical University of South Carolina, Charleston (Hughes-Halbert); American Board of Otolaryngology, Houston, Texas (Nussenbaum).

Abstract

IMPORTANCE—Delays in the delivery of care for head and neck cancer (HNC) are a key driver of poor oncologic outcomes and thus represent an important therapeutic target.

OBJECTIVE—To synthesize information about the association between delays in the delivery of care for HNC and oncologic outcomes.

EVIDENCE REVIEW—A systematic review of the English-language literature in PubMed/MEDLINE and Scopus published between January 1, 2007, and February 28, 2018, was performed to identify articles addressing the association between treatment delays and oncologic outcomes for patients with HNC. Articles that were included (1) addressed cancer of the oral cavity, oropharynx, hypopharynx, or larynx; (2) discussed patients treated in 2004 or later; (3) analyzed time of diagnosis to treatment initiation (DTI), time from surgery to the initiation of

Corresponding Author: Evan M. Graboyes, MD, Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, 135 Rutledge Ave, Mail Stop Center 550, Charleston, SC 29425 (graboyes@musc.edu).

Author Contributions: Dr Graboyes and Mr Kompelli had full access to all the data in the study and take responsibility for the integrity ofthe data and the accuracy of the data analysis.

Concept and design: Kompelli, Neskey, Nguyen, Hughes-Halbert.

Acquisition, analysis, or interpretation of data: Graboyes, Kompelli, Brennan, Nguyen, Sterba, Warren, Nussenbaum, Day.

Drafting of the manuscript: Graboyes, Kompelli, Brennan, Nguyen, Day.

Critical revision of the manuscript for important intellectual content: Graboyes, Kompelli, Neskey, Sterba, Warren, Hughes-Halbert, Nussenbaum, Day.

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postoperative radiotherapy, and/or treatment package time (TPT; the time from surgery through the completion of postoperative radiotherapy); (4) included a clear definition of treatment delay; and (5) analyzed the association between the treatment time interval and an oncologic outcome measure. Quality assessment was performed using the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies.

FINDINGS—A total of 18 studies met inclusion criteria and formed the basis of the systematic review. Nine studies used the National Cancer Database and 6 studies were single-institution retrospective reviews. Of the 13 studies assessing DTI, 9 found an association between longer DTI and poorer overall survival; proposed DTI delay thresholds ranged from more than 20 days to 120 days or more. Four of the 5 studies assessing time from surgery to the initiation of postoperative radiotherapy (and all 4 studies assessing guideline-adherent time to postoperative radiotherapy) found an association between a timely progression from surgery to the initiation of postoperative radiotherapy and improved overall or recurrence-free survival. Of the 5 studies examining TPT, 4 found that prolonged TPT correlated with poorer overall survival; proposed thresholds for prolonged TPT ranged from 77 days or more to more than 100 days.

CONCLUSIONS AND RELEVANCE—Timely care regarding initiation of treatment, postoperative radiotherapy, and TPT is associated with survival for patients with HNC, although significant heterogeneity exists for defining delayed DTI and TPT. Further research is required to standardize optimal time goals, identify barriers to timely care for each interval, and design interventions to minimize delays.

Head and neck cancer (HNC) is the sixth most common cancer worldwide, with 630 000 new diagnoses annually and 350 000 deaths per year.[1] In the United States, more than 65 000 patients are diagnosed with HNC each year, and HNC causes more than 14000 deaths per year.[2] No screening tests exist for HNC, and more than two-thirds of patients present with locally advanced disease. Despite aggressive multimodality therapy using combinations of surgery, radiotherapy, and chemotherapy, oncologic outcomes remain poor. As a result, there is a critical need to identify strategies to improve survival for patients with HNC.

One strategy to improve survival for patients with HNC focuses on improving the timeliness of care delivery. Timeliness of care is a primary indicator of health care quality and is used as a measure of the quality of oncology care.[3–5] Timely HNC care has been assessed along the treatment continuum from symptom onset to consultation,[6] referral to consultation,[7–9] diagnosis to treatment initiation (DTI),[10–12] surgery to initiation of postoperative radio therapy (S-PORT),[13–16] and treatment package time (TPT; the time from surgery through the completion of postoperative radiotherapy).[17–20] Across the continuum of HNC care delivery, delays are common,[13] are a major source of preventable mortality,[18] and contribute to suboptimal survival.[12] Of these measures of timely care, S-PORT is the only one included in the National Comprehensive Cancer Network Guidelines for HNC, for which the recommended time interval between surgery and PORT is 6 weeks or less.[21] Nevertheless, DTI,[12] S-PORT,[13,15] and TPT[16,18,19] have all been suggested as quality indicators for HNC.

Because delivering timely HNC care is increasingly recognized as critical to achieving optimal oncologic outcomes, there has been a proliferation of studies addressing this topic in recent years.[10,14,18–20,22] These studies have addressed delays at different points along the

treatment continuum, focused on different subsites, used different data sources, defined delay using different methods, and correlated delays with different outcomes. The volume of studies and heterogeneity in study design has made understanding the literature challenging and prevented implementation of best practices into clinical care. The goal of this systematic review is thus to summarize the evidence about the association of 3 measures of timely HNC care (DTI, S-PORT, and TPT) with oncologic outcomes for patients with HNC.

Methods

Information Sources, Search Strategy, and Study Selection

Asenior medical librarian (E.B.) designed a comprehensive search strategy for published literature to identify English-language articles related to treatment delay in HNC. Information sources included PubMed/MEDLINE and Scopus. The search strategy was performed between January 24 and March 1, 2018, in an iterative fashion to refine search criteria. The final search strategy used the following key words and/or combinations of Medical Subject Heading terms: “head and neck neoplasms,” “head and neck cancer,” “head and neck squamous cell cancer,” “oral cancer,” “mouth neoplasms,” “laryngeal neoplasms,” “gingival neoplasms,” “oral leukoplakia,” “lip neoplasms,” “palatal neoplasms,” “tongue neoplasms,” “pharyngeal neoplasms,” “squamous,” “time-to-treatment,” “time-to-initiation,” “treatment initiation,” “treatment delay,” “treatment time,” “timely care,” “diagnosis-to-treatment,” “treatment package,” “quality of care,” “timely care,” and “time factors.” We limited our search to articles published between January 1, 2007, and February 28, 2018 (and then included articles with at least part of the cohort treated after 2004), to reflect the paradigm shift and updated practice patterns of the era of adjuvant chemoradiotherapy[23,24] and modern radiotherapy techniques, such as intensity-modulated radiotherapy,[25,26] which have been hypothesized to moderate the association between treatment delays and oncologic outcomes.[16,19,20] The Preferred Reporting Items for Systematic Reviews and Meta analyses (PRISMA) guidelines were used for reportingthroughout.[27] No review protocol exists for this study.

The study inclusion criteria are shown in the Box. Because the purpose of the review is to address the delivery of timely HNC care, we elected not to include studies analyzing the association of radiation treatment time with survival. The rationale for this exclusion is that radiation treatment time (especially in the definitive setting) is affected by 2 fundamentally different factors: altered fractionation schedules and unintended treatment breaks. Studies assessing TPT were included in the analysis, however, because altered fractionation is rarely used in the adjuvant setting, and health care delivery factors associated with starting PORT are a critically important determinant of TPT. Abstracts without full articles available for review were also excluded. After the initial search, candidate abstracts were reviewed by one of us (A.R.K.) and full-text articles were independently assessed for eligibility by 2 of us (E.M.G.and A.R.K.). Two of us (E.M.G. and A.R.K.) searched the reference lists of the included publications to identify additional articles.

Data Items and Data Collection Process

Variables to be extracted and categorization definitions were defined a priori. The primary variables of interest were measures of timely HNC care delivery: DTI, S-PORT, and TPT. If a study addressed more than 1 facet of timely care (eg, DTI and TPT), each aspect of timely care was analyzed. The following variables were abstracted from each article: publication year, country, definition of delay, derivation of delay definition, data source (categorized as single-institution or multi-institutional study, cancer registry, or population-based), year of diagnosis, treatment, sample size, frequency of delay, oncologic and treatment characteristics (HNC subsite, American Joint Committee on Cancer stage grouping, and treatment modality), and association of delay with survival. The derivation of the definition of delay was categorized using the following taxonomy: prespecified (eg adherent to National Comprehensive Cancer Network Guidelines for time to PORT), descriptively based (eg, based on the median or quartiles of the study sample), derived (eg, from recursive partition analysis), or unspecified. No attempts were made to contact investigators to clarify missing information. Data collection and analysis was performed between March 1 and August 8, 2018.

Outcome measures included overall survival (OS), disease-specific survival (DSS), disease-free survival (also referred to as *recurrence-free survival)*, and locoregional control, although only 4 of the 18 studies provided measures other than OS. The association of the explanatory variable of interest (DTI, S-PORT, TPT) with the outcome measure (eg, OS) was expressed as an adjusted hazard ratio (aHR) and 95% CI if the study authors performed a multivariable Cox proportional hazards regression analysis. In situations in which less information was presented (eg, median OS, P values only), the data were tabulated.

Data Analysis and Synthesis of Results

Given the continuous nature of time-to-treatment data but the heterogeneity in reporting of categorical time-to-treatment thresholds as well as the vast differences in the thoroughness of covariate adjustment performed in each Cox proportional hazards regression analysis, we elected to perform a systematic review instead of a meta-analysis. Although combining these types of data in meta-regressions is technically possible and techniques for doing so have been described,[28] we believed that reporting meta-regressions for timely care thresholds would obscure important differences in threshold heterogeneity and falsely convey a certainty about the interpretation of the data that does not exist. Thus, data are tabulated, presented, and summarized but not combined into pooled HRs.

Quality Assessment

All studies were case series or cohort studies, so the Institute of Health Economics Quality Appraisal Checklist for Case Series Studies was used to assess quality.[29] The minimum quality score is 0 and the maximum quality score is 20, with higher scores indicating higher quality (eTable in the Supplement). Quality analysis was performed independently by 2 of us (E.M.G. and A.R.K.), and differences in ratings were resolved by consensus.

Results

Description of Studies

The PRISMA flow diagram showing derivation of the included articles is shown in the eFigure in the Supplement. Using the comprehensive search terms, 1135 unique abstracts were identified and screened, 59 were reviewed in full to assess eligibility, and 18 were included in the analysis. Review of references from these manuscripts revealed no additional articles. Assessment of quality was performed using the Institute of Health Economics Quality Appraisal Check list for Case Series Studies.[29] The studies ranged in quality from 10 to 13 (on a scale of 0–20). All studies were retrospective, using registry (9 studies used the National Cancer Database) or single institution data as a source. The earliest analyzed cohort included patients treated from 1998 to 2011; 11 of the studies (61%) included patients treated exclusively in 2004 or later.

Diagnosisto Treatment Initiation

Thirteen articles addressing DTI were included in the analysis (Table1).[10,19,22,30–39] These articles were primarily published in 2016 or later (10 [77%])[10,19,22,30–36] and were set in the United States (7 [54%]).[10,19,22,30,34,36,39] The articles generally used cancer registry data as a data source (9 [69%])[10,22,30–35,37,38]; as a result, the sample sizes were large (>1500 patients). Six studies (46%)[10,33,36–39] included all head and neck subsites, while 7 studies (54%) were subsite specific (5 oral cavity, 1 oropharynx, and 1 larynx).[19,22,30–32,34,35] Four of the studies (31%)[22,31,33,36] did not define the rationale or methods for their definition of prolonged DTI, 4 (31%)[19,35,37,38] used calendar-based categorical definitions (eg, <30 days, 31–60 days), 3 (23%)[30,34,39] used cohort-based quartiles or medians, and 2 (15%)[10,32] used recursive partition analysis to determine an optimal DTI threshold. One study, which exclusively examined cancer of the oral cavity, suggested that DTI of less than 20 days was optimal.[32] The other study, which included all subsites, proposed that optimal treatment should begin within 46 to 52 days of diagnosis.[10] An association between delays in DTI and poorer oncologic outcomes was observed in 9 studies (69%).[10,22,31–37] The delayed DTI threshold varied from more than 20 days to 120 days or more. The 4 studies that did not find an association between DTI and survival analyzed thresholds of 50 days or more (vs 24days or less), 45 days or more (vs 30 days or less), and more than 30 days (vs 30 days or less; analyzed in 2 studies).[19,30,38,39] The effect size of DTI on survival generally increased with longer DTI intervals, consistent with studies in which DTI was analyzed as a continuous variable.

S-PORT Interval

The S-PORT interval was analyzed in 5 articles (Table 2).[14,15,19,20,30] All were published in 2017 or later and set in the United States. Four studies[14,15,20,30] used cancer registry data and 1 study[19] used a single institution design. Four studies[14,15,19,20] found an association between delays in the S-PORT interval and poorer oncologic outcomes. The only study that did not find an association between timely S-PORT and survival used study cohort quartiles to define delayed PORT (≥ 64 days vs <50 days)[30] instead of National Comprehensive Cancer Network Guideline recommendations (≤ 6 weeks vs >6 weeks). The effect sizes for timely, guideline-adherent SPORT on OS were similar between studies (aHR, 1.10–1.13 for

>6 weeks vs ≤ 6 weeks; aHR, 0.93 for ≤ 6 weeks vs > 6 weeks), although 3 of the 4 studies[14,15,19,20] used the National Cancer Database as a data source. The effect size of delayed PORT on recurrence-free survival in the single institution study was 2.42 (>6 weeks relative to ≤ 6 weeks).[19] Only 1 study assessed the association between SPORT and survival in a nondichotomized fashion, reporting progressive survival decrements with increasing S-PORT intervals (aHR, 1.09 for S-PORT of 7–8 weeks; aHR, 1.10 for S-PORT of 8–10 weeks; and aHR, 1.12 for S-PORT of >10 weeks).[14]

Treatment Package Time

Five studies analyzed TPT (Table 3).[18–20,30,40] All of these articles were published in 2016 or later and 4[18–20,30] were set in the United States. Three articles[18,20,30] used a national cancer registry as a data source and 2 were single-institution studies.[19,40] Three studies[18,20,40] included a heterogeneous grouping of head and neck subsites and 2 were subsite specific (oral cavity).[19,30] Of the 5 studies, 4 found an association between prolonged TPT and poorer oncologic outcomes.[18–20,40] The 1 study that did not find an association between TPT and survival compared a TPT threshold of 161 days or more with a TPT threshold of less than 136 days.[30] In the studies that found an association between prolonged TPT and poorer survival, the threshold at which prolonged TPT correlated with poorer oncologic outcomes varied from 11 weeks or more (77 days) to 100 days or more.[18–20,40] The definition of delay was determined by recursive partition analysis in 2 TPT studies,[20,40] not specified in 2,[18,19] and determined by cohort quartiles in the other study.[30] Of the 2 studies that attempted to define an optimal TPT using either recursive partition analysis or decision tree analysis, their proposed thresholds were 87 days or more and more than 97 days.[20,40] In the studies in which TPT was associated with OS, effect sizes were highly variable and ranged from 1.07 (≤13 weeks vs >13 weeks) to 6.7 (≤11 weeks vs >11 weeks).[18–20,40] Only 1 study using nondichotomized definitions of delay showed an association between increasingly prolonged TPT and progressive decrements in survival (aHR, 1.19 for 11–12 weeks; aHR, 1.36 for 13–15 weeks; and aHR, 1.51 for ≥ 16 weeks relative to <11 weeks).[18]

Discussion

In this systematic review, we analyzed 3 different measures of timely care for patients with HNC (DTI, S-PORT, and TPT). Each measure was highly correlated with survival despite differences in study design, patient population, and definitions of delay.

Diagnosis to Treatment Initiation

Diagnosis to treatment initiation was the most frequently studied measure of timely HNC care in this review, addressed in a variety of head and neck subsites, and assessed in the United States, Europe, and Asia. Of the 3 measures of timely care, DTI was the most variable in its definition of delay and association with survival (delay thresholds ranging from >20 days to ≥120 days). As a measure of timely initiation of treatment, DTI is imperfect because it fails to capture relevant time between symptom onset and pathologic diagnosis. Access to care issues related to rural geography, race/ethnicity, insurance, and other social determinants of health that may delay entry into the health care system to obtain

a diagnosis thus may not be fully captured by measures assessing DTI. Despite heterogeneity in definitions of delayed DTI, most studies included in this review did find an association between prolonged DTI and decreased survival,[10,22,31,32] although 1 study found an association only at the extreme DTI interval with no association between DTI and survival for the intermediate categories.[33]

The mechanism by which prolonged DTI influences survival is not known, but data support the role of stage migration as the proximate cause.[12] Because stage and subsite might confound the association between prolonged DTI and survival, nearly all studies adjusted for stage and subsite in their multivariable Cox proportional hazards regression models. In addition, 1 study described an interaction between American Joint Committee on Cancer stage and tumor site with DTI and survival.[10] In subgroup effects interaction testing, the mortality risk for prolonged DTI was more pronounced for early-stage disease and in patients with oropharyngeal cancer.[10]

Reasons for delay have been ascribed to patient factors (eg, failure to recognize that symptoms are due to cancer) and professional factors (eg, scheduling additional imaging or tests). Issues related to prolonged DTI seem more pronounced at academic medical centers in which patients often receive a diagnosis prior to referral and transition of care to the academic center.[10] Effective strategies to improve DTI for patients with HNC nevertheless remain unknown. Patient navigation is 1 strategy to improve timely cancer care that is well supported by high-quality evidence for screening and treatment initiation for other oncologic sites.[41–44] However, there is a dearth of data about the association of patient navigation with timely initiation of treatment for patients with HNC.[45,46] Whether patient navigation can decrease delays initiating treatment for HNC is a question that merits further research.

S-PORT Interval

The S-PORT interval is the only measure of timely care in the National Comprehensive Cancer Network Guidelines for HNC.[21] Guidelines recommend that PORT commence within 6 weeks of surgery.[21] A meta-analysis published 15 years ago substantiated the association between delays starting PORT for patients with HNC and poorer oncologic outcomes.[47] The data from our systematic review provide continued support that starting PORT within 6 weeks or less of surgery is associated with improved survival even in the era of intensity-modulated radiation therapy and concurrent systemic therapy.[14,15,19,20] For these reasons, S-PORT has been proposed as a quality measure for HNC,[15] and benchmark targets for timely S-PORT have been proposed.[48]

The mechanism by which delays starting PORT affect survival are hypothesized to occur through repopulation and proliferation of residual microscopic disease and tumor clonogens,[49] which is accelerated postoperatively after population depletion.[50] Mathematical models suggest that persistent, postoperative microscopic tumor clonogens repopulate with a doubling time of 40 to 45 days.[51] 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 PORT.[51,52]

Despite the association between delays starting PORT and poorer survival, delays starting PORT are common nationally. One study described that 56% of patients with HNC undergoing surgery followed by adjuvant therapy start PORT more than 6 weeks after surgery.[13] Delays starting PORT disproportionately burden racial/ethnic minorities, those with Medicaid or no insurance, and those of low socioeconomic status.[13] The patient-level barriers to timely initiation of PORT and effective strategies to address these barriers in medically vulnerable patients are unknown. In addition, optimal strategies to mitigate the wound complications and unplanned hospital read missions that can contribute to delays starting PORT are uncertain. However, 1 promising single institution study provided preliminary data that using quality improvement methods to target key process-of-care drivers for delayed PORT (timely dental consultation, timely radiation oncology consultations, and patient engagement) can decrease delays starting PORT.[48] Future research is required to identify whether this strategy can be generalized and implemented at other institutions to achieve similar improvements in timely PORT. In addition, whether interventions aimed at improving S-PORT can be applied to other time intervals along the HNC care continuum in which delays are noted is important and should be addressed in future research.

Treatment Package Time

Like other measures of timely care, TPT has been proposed as a quality metric for patients with HNC. Some argue that TPT is more prognostically important than S-PORT.[16,18,19] Data from this systematic review support the association between prolonged TPT and poorer oncologic outcomes. However, unlike the time interval for S-PORT (which is agreed to be ≤ 6 weeks), significant heterogeneity exists for defining timely TPT.[18,20] Treatment package time was defined in a dichotomous fashion in all but 2 of the studies in this analysis, with the following oncologically relevant proposed, prolonged TPT intervals: 11 weeks or more, more than 11 weeks, 87 days or more, and more than 13 weeks. The 2 studies that attempted to derive an optimal TPT were all within 2 weeks of one another (<87 to ≤97 days). If TPT is to be used as a quality metric for HNC,[19] additional work will be required to achieve consensus regarding optimal TPT from the variety of proposed definitions.

Treatment package time encompasses S-PORT as well as the interval of delivering adjuvant therapy. Causes of prolonged TPT therefore include all of those present for S-PORT plus additional challenges for timely completion of adjuvant therapy. The barriers to timely S-PORT, which reflect issues related to postoperative complications, care coordination, timely radiation oncology consultation, and patient engagement,[48] are qualitatively different than the barriers that cause treatment breaks during adjuvant therapy. Barriers to timely completion of (chemo) radiotherapy, whether in the definitive or adjuvant setting, primarily include issues related to acute toxic effects of treatment and high symptom burden secondary to mucositis, dehydration, malnutrition, and pain, as well as hemato logic complications.[16,53,54] Strategies to improve TPT will likely have to use 1 set of strategies to improve the S-PORT aspect of TPT and a different set of interventions to decrease the frequency and duration of treatment breaks during (chemo)radiotherapy.

Limitations

This study has some limitations. We excluded non-English-language articles, which could bias our results. We did not include unpublished posters, conference proceedings, or other non-peer-reviewed sources, which could cause publication bias.[27,55] The studies analyzed and described herein are heterogeneous with respect to data source, country, study setting, design, definition of delay, patient population, and outcome measures. Owing to heterogeneity in the reporting of outcome measures, we merged data related to OS, DSS, recurrence-free survival, and locoregional control, which could affect our findings. Although the studies were generally in agreement in terms of the direction and magnitude of their findings with respect to delays and survival, the applicability of one study's findings to another clinical setting is unknown. The data in this review are not granular enough to address referral patterns, care pathways, treatment algorithms, and details of treatments such as type of surgery (eg, robotic), radiotherapy (eg, intensity-modulated radiation therapy), or systemic therapy, which likely vary significantly across institutions and countries. In addition, details regarding wound healing and flap complications, unplanned surgery, hospital readmission, and other factors that contribute to delayed S-PORT and prolonged TPT were rarely included in the studies and thus not analyzed as part of this systematic review. We also did not address the association between timely HNC care and disparities in HNC outcomes that have been well described in prior studies.[13,18,36] Given limitations of reported data, we were unable to provide a quantitative synthesis of the published timely care intervals.

Future studies addressing timely HNC care should address these limitations. Especially given the heterogeneity in proposed optimal DTI and TPT cutoffs, the lack of quantitative synthesis prevents generalizing to optimal treatment time intervals and generating consensus treatment time benchmarks. We did not address the frequency of delays in care; patient-level, clinician-level, or system-level barriers to timely care; or strategies to improve timely care. These are all critically important topics that merit future study. We analyzed only the association of timely care across 3 time intervals (DTI, S-PORT, and TPT) but acknowledge that other measures of timely HNC care exist (including radiotherapy treatment time) and are important for optimizing outcomes. This review analyzed only the association of delays in care with survival. Other relevant outcome measures include cost, cost-effectiveness, patient perceptions of quality, patient anxiety and distress, and clinician anxiety and distress.

Conclusions

Timely care related to initiation of treatment, postoperative radio therapy, and TPT is associated with survival for patients with HNC. There is a significant heterogeneity in the definition of delay for DTI and TPT, which prevents benchmarking and should be addressed in future studies. In addition, more research is required to address knowledge gaps related to the identification of barriers to timely care across the cancer care continuum as well as design and implementation of interventions to improve timely HNC care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55(2): 74–108. doi:10.3322/canjclin.55.2.74 [PubMed: 15761078]
2. American Cancer Society. Cancer facts & figures: 2018 https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed February 262018.
3. Hewitt M, Simone J. National Cancer Policy Board: Ensuring Quality Cancer Care. Washington, DC: The National Academies Press; 1999.
4. Committee on Quality of Health Care in America, Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academy Press; 2001.
5. Bolwell BJ, Khorana AA. Enhancing value for patients with cancer: time to treatment as a surrogate for integrated cancer care. J Natl Compr Canc Netw. 2016;14(1):115–116. doi:10.6004/jnccn.2016.0010 [PubMed: 26733558]
6. Carroll WR, Kohler CL, Carter VL, Hannon L, Skipper JB, Rosenthal EL. Barriers to early detection and treatment of head and neck squamous cell carcinoma in African American men. Head Neck. 2009;31(12):1557–1562. doi:10.1002/hed.21125 [PubMed: 19431197]
7. Graboyes EM, Gross J, Kallogjeri D, et al. Association of compliance with process-related quality metrics and improved survival in oral cavity squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg. 2016;142(5):430–437. doi:10.1001/jamaoto.2015.3595 [PubMed: 26869135]
8. Graboyes EM, Townsend ME, Kallogjeri D, Piccirillo JF, Nussenbaum B. Evaluation of quality metrics for surgically treated laryngeal squamous cell carcinoma. JAMA Otolaryngol Head Neck Surg. 2016;142(12):1154–1163. doi:10.1001/jamaoto.2016.0657 [PubMed: 27435696]
9. Pitchers M, Martin C. Delay in referral of oropharyngeal squamous cell carcinoma to secondary care correlates with a more advanced stage at presentation, and is associated with poorer survival. Br J Cancer. 2006;94(7):955–958. doi:10.1038/sj.bjc.6603044 [PubMed: 16552440]
10. Murphy CT, Galloway TJ, Handorf EA, et al. Survival impact of increasing time to treatment initiation for patients with head and neck cancer in the United States. J Clin Oncol. 2016;34(2): 169–178. doi:10.1200/JCO.2015.61.5906 [PubMed: 26628469]
11. Murphy CT, Galloway TJ, Handorf EA, et al. Increasing time to treatment initiation for head and neck cancer: an analysis of the National Cancer Database. Cancer. 2015;121(8):1204–1213. doi: 10.1002/cncr.29191 [PubMed: 25490875]
12. Xiao R, Ward MC, Yang K, et al. Increased pathologic upstaging with rising time to treatment initiation for head and neck cancer: a mechanism for increased mortality. Cancer. 2018;124(7): 1400–1414. doi:10.1002/cncr.31213 [PubMed: 29315499]
13. Graboyes EM, Garrett-Mayer E, Sharma AK, Lentsch EJ, Day TA. Adherence to National Comprehensive Cancer Network guidelines for time to initiation of postoperative radiation therapy for patients with head and neck cancer. Cancer. 2017; 123(14):2651–2660. doi:10.1002/cncr.30651 [PubMed: 28241092]
14. Graboyes EM, Garrett-Mayer E, Ellis MA, et al. Effect of time to initiation of postoperative radiation therapy on survival in surgically managed head and neck cancer. Cancer. 2017;123(24): 4841–4850. doi:10.1002/cncr.30939 [PubMed: 28841234]
15. Cramer JD, Speedy SE, Ferris RL, Rademaker AW, Patel UA, Samant S. National evaluation of multidisciplinary quality metrics for head and neck cancer. Cancer. 2017;123(22):4372–4381. doi: 10.1002/cncr.30902 [PubMed: 28727137]

16. Shaikh T, Handorf EA, Murphy CT, Mehra R, Ridge JA, Galloway TJ. The impact of radiation treatment time on survival in patients with head and neck cancer. Int J Radiat Oncol Biol Phys. 2016; 96(5):967–975. doi:10.1016/j.ijrobp.2016.08.046 [PubMed: 27869097]
17. Rosenthal DI, Liu L, Lee JH, et al. Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. Head Neck. 2002; 24(2):115–126. doi:10.1002/hed.10038 [PubMed: 11891941]
18. Guttmann DM, Kobie J, Grover S, et al. National disparities in treatment package time for resected locally advanced head and neck cancer and impact on overall survival. Head Neck. 2018;40(6): 1147–1155. doi:10.1002/hed.25091 [PubMed: 29394465]
19. Chen MM, Harris JP, Orosco RK, Sirjani D, Hara W, Divi V. Association of time between surgery and adjuvant therapy with survival in oral cavity cancer. Otolaryngol Head Neck Surg. 2018;158(6): 1051–1056. doi:10.1177/0194599817751679 [PubMed: 29313448]
20. Tam M, Wu SP, Gerber NK, et al. The impact of adjuvant chemoradiotherapy timing on survival of head and neck cancers [published online February 26, 2018]. Laryngoscope. 2018. doi:10.1002/lary.27152
21. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Head and Neck Cancels. Fort Washington, PA: National Comprehensive Cancer Network; 2017.
22. Cheraghlou S, Kuo P, Judson BL. Treatment delay and facility case volume are associated with survival in early-stage glottic cancer. Laryngoscope. 2017;127(3):616–622.doi:10.1002/lary.26259 [PubMed: 27653749]
23. Cooper JS, Pajak TF, Forastiere AA, et al.; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937–1944. doi:10.1056/NEJMoa032646 [PubMed: 15128893]
24. Bernier J, Domenge C, Ozsahin M, et al.; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945–1952.doi:10.1056/NEJMoa032641 [PubMed: 15128894]
25. Guadagnolo BA, Liu CC, Cormier JN, Du XL. Evaluation of trends in the use of intensity-modulated radiotherapy for head and neck cancer from 2000 through 2005: socioeconomic disparity and geographic variation in a large population-based cohort. Cancer. 2010;116(14): 3505–3512. doi:10.1002/cncr.25205 [PubMed: 20564123]
26. Sher DJ, Neville BA, Chen AB, Schrag D. Predictors of IMRT and conformal radiotherapy use in head and neck squamous cell carcinoma: aSEER-Medicare analysis. Int J Radiat Oncol Biol Phys. 2011;81(4):e197–e206. doi:10.1016/j.ijrobp.2011.02.007 [PubMed: 21596483]
27. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4): 264–269, W64. doi:10.7326/0003-4819-151-4-200908180-00135 [PubMed: 19622511]
28. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559–1573. doi:10.1002/sim.1187 [PubMed: 12111920]
29. Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. J Clin Epidemiol. 2016;69:199–207.e2. doi:10.1016/j.jclinepi.2015.07.010 [PubMed: 26307459]
30. Fujiwara RJ, Judson BL, Yarbrough WG, Husain Z, Mehra S. Treatment delays in oral cavity squamous cell carcinoma and association with survival. Head Neck. 2017;39(4):639–646. doi: 10.1002/hed.24608 [PubMed: 28236349]
31. Tsai WC, Kung PT, Wang YH, Huang KH, Liu SA. Influence of time interval from diagnosis to treatment on survival for oral cavity cancer: a nationwide cohort study. PLoS One. 2017;12(4): e0175148.doi:10.1371/journal.pone.0175148 [PubMed: 28388649]
32. Liao CT, Chen HN, Wen YW, et al. Association between the diagnosis-to-treatment interval and overall survival in Taiwanese patients with oral cavity squamous cell carcinoma. Eur J Cancer. 2017; 72:226–234. doi:10.1016/j.ejca.2016.11.010 [PubMed: 28056426]

33. Polesel J, Furlan C, Birri S, et al. The impact of time to treatment initiation on survival from head and neck cancer in north-eastern Italy. Oral Oncol. 2017;67:175–182. doi:10.1016/j.oraloncology.2017.02.009 [PubMed: 28351574]
34. Sharma S, Bekelman J, Lin A, et al. Clinical impact of prolonged diagnosis to treatment interval (DTI) among patients with oropharyngeal squamous cell carcinoma. Oral Oncol. 2016;56: 17–24. doi:10.1016/j.oraloncology.2016.02.010 [PubMed: 27086482]
35. Chiou SJ, Lin W, Hsieh CJ. Assessment of duration until initial treatment and its determining factors among newly diagnosed oral cancer patients: a population-based retrospective cohort study. Medicine (Baltimore). 2016;95(50):e5632. doi:10.1097/MD.0000000000005632 [PubMed: 27977607]
36. Naghavi AO, Echevarria MI, Strom TJ, et al. Treatment delays, race, and outcomes in head and neck cancer. Cancer Epidemiol. 2016;45:18–25. doi:10.1016/j.canep.2016.09.005 [PubMed: 27664388]
37. van Harten MC, Hoebers FJ, Kross KW, van Werkhoven ED, van den Brekel MW, van Dijk BA. Determinants of treatment waiting times for head and neck cancer in the Netherlands and their relation to survival. Oral Oncol. 2015;51(3):272–278. doi:10.1016/j.oraloncology.2014.12.003 [PubMed: 25541458]
38. van Harten MC, de Ridder M, Hamming-Vrieze O, Smeele LE, Balm AJ, van den Brekel MW. The association of treatment delay and prognosis in head and neck squamous cell carcinoma (HNSCC) patients in a Dutch comprehensive cancer center. OralOncol. 2014;50(4):282–290. doi:10.1016/j.oraloncology.2013.12.018
39. Caudell JJ, Locher JL, Bonner JA. Diagnosis-to-treatment interval and control of locoregionally advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 2011;137(3): 282–285. doi:10.1001/archoto.2011.20 [PubMed: 21422314]
40. Tribius S, Donner J, Pazdyka H, et al. Survival and overall treatment time after postoperative radio (chemo) therapy in patients with head and neck cancer. Head Neck. 2016;38(7):1058–1065. doi:10.1002/hed.24407 [PubMed: 26873810]
41. Battaglia TA, Bak SM, Heeren T, et al. Boston Patient Navigation Research Program: the impact of navigation on time to diagnostic resolution after abnormal cancer screening. Cancer Epidemiol Biomarkers Prev. 2012;21(10):1645–1654. doi:10.1158/1055-9965.EPI-12-0532 [PubMed: 23045539]
42. Paskett ED, Katz ML, Post DM, et al.; Ohio Patient Navigation Research Program. The Ohio Patient Navigation Research Program: does the American Cancer Society patient navigation model improve time to resolution in patients with abnormal screening tests? CancerEpidemiol Biomarkers Prev. 2012;21(10):1620–1628. doi:10.1158/1055-9965.EPI-12-0523
43. Dudley DJ, Drake J, Quinlan J, et al. Beneficial effects of a combined navigator/promotora approach for Hispanic women diagnosed with breast abnormalities. Cancer Epidemiol Biomarkers Prev. 2012;21(10):1639–1644. doi:10.1158/1055-9965.EPI-12-0538 [PubMed: 23045538]
44. Freund KM, Battaglia TA, Calhoun E, et al.; Writing Group of the Patient Navigation Research Program. Impact of patient navigation on timely cancer care: the Patient Navigation Research Program. J Natl Cancer Inst. 2014;106(6):dju115. doi:10.1093/jnci/dju115 [PubMed: 24938303]
45. Fillion L, de Serres M, Cook S, Goupil RL, Bairati I, Doll R. Professional patient navigation in head and neck cancer. Semin Oncol Nurs. 2009;25(3):212–221. doi:10.1016/j.soncn.2009.05.004 [PubMed: 19635400]
46. Ohlstein JF, Brody-Camp S, Friedman S, Levy JM, Buell JF, Friedlander P. Initial experience of a patient navigation model for head and neck cancer. JAMA Otolaryngol Head Neck Surg. 2015;141(9): 804–809. doi:10.1001/jamaoto.2015.1467 [PubMed: 26313895]
47. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? a systematic review. J Clin Oncol. 2003;21(3):555–563. doi:10.1200/JCO.2003.04.171 [PubMed: 12560449]
48. Divi V, Chen MM, Hara W, et al. Reducing the time from surgery to adjuvant radiation therapy: an institutional quality improvement project. Otolaryngol Head Neck Surg. 2018;159(1):158–165. doi:10.1177/0194599818768254 [PubMed: 29631478]

49. Mackillop WJ, Bates JH, O'Sullivan B, Withers HR. The effect of delay in treatment on local control by radiotherapy. IntJ Radiat Oncol Biol Phys. 1996; 34(1):243–250.doi: 10.1016/0360-3016(95)02049-7 [PubMed: 12118558]
50. Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer—the time factor. IntJ Radiat Oncol Biol Phys. 1997;39(4):831–836. doi: 10.1016/S0360-3016(97)00466-5 [PubMed: 9369130]
51. Al-Dweri FM, Guirado D, Lallena AM, Pedraza V. Effect on tumour control of time interval between surgery and postoperative radiotherapy: an empirical approach using Monte Carlo simulation. Phys Med Biol. 2004;49(13):2827–2839. doi:10.1088/0031-9155/49/13/005 [PubMed: 15285250]
52. Suwinski R, Sowa A, Rutkowski T, Wydmanski J, Tarnawski R, Maciejewski B. Time factor in postoperative radiotherapy: a multivariate locoregional control analysis in 868 patients. IntJ Radiat Oncol Biol Phys. 2003;56(2):399–412. doi:10.1016/S0360-3016(02)04469-3 [PubMed: 12738315]
53. Russo G, Haddad R, Posner M, Machtay M. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist. 2008;13(8):886–898. doi:10.1634/theoncologist.2008-0024 [PubMed: 18701763]
54. Thomas K, Martin T, Gao A, Ahn C, Wilhelm H, Schwartz DL. Interruptions of head and neck radiotherapy across insured and indigent patient populations. J Oncol Pract. 2017;13(4):e319–e328. doi:10.1200/JOP.2016.017863 [PubMed: 28267393]
55. Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: a literature analysis. PLoS Med. 2008;5(9):e191. doi:10.1371/journal.pmed.0050191 [PubMed: 18816163]

Key Points

Question

What is the association between treatment delay and oncologic outcomes for patients with head and neck cancer?

Findings

In this systematic review, treatment delay across the cancer care continuum (diagnosis to treatment initiation, surgery to the initiation of postoperative radiotherapy, and treatment package time) was associated with poorer survival for patients with head and neck cancer. Significant heterogeneity exists for defining delayed diagnosis to treatment interval and treatment package time.

Meaning

Efforts should be made to optimize timely head and neck cancer care across the treatment continuum; further research is required to standardize optimal time goals, identify barriers to timely care for each interval, and design interventions to minimize delays.

Box. Inclusion Criteria for Articles Selected for Review

Site: patients underwent treatment for a diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.

Diagnosis and treatment dates: at least part of the cohort was treated after 2004.

Time interval: clear statement that the time interval of care being measured involved time from diagnosis to treatment initiation, surgery to the initiation of postoperative radiotherapy, and/or total treatment package time.

Definition of delay: clear statement of how authors defined delay.

Outcome measure: clear statement that the authors were assessing the association between the treatment time interval and an oncologic outcome (eg, overall survival, recurrence).

Table 1.

Diagnosis to Treatment Initiation (DTI)

Source	Country	Definition of Delayed DTI	Derivation of Definition of Delay	Data Source	Sample Size, No.	Years of Diagnosis or Treatment	Freq of Delay, %	HN Subsite, %	AJCC Stage Grouping,%	Treatment Modality, %	Association of Delay to Survival, aHR(95%CI)	Quality Score
Chen et al,[19] 2018	United States	>30 d	Calendar-based (1 mo)	Single academic medical center	132	2008–2016	NR	OC: 100	Pathologic I: 7 II: 18 III: 12 IV: 63	S + RT: 63 S + CRT: 37	OS ≤30 d, 1 [Ref] >30 d, 1.07 (0.43–2.67) RFS ≤30 d, 1 [Ref] >30 d, 1.55 (0.73–3.29)	11
Cheraghlou et al,[22] 2017	United States	>100 d	Not specified	National sample of CoC-accredited hospitals	5627	2004–2012	>100 d: 1	Lx: 100	Clinical I: 50 II: 50	S: 11 S + RT: 19 RT: 69	OS ≤100 d, 1 [Ref] >100 d: 1.6 (NR)	11
Fujiwara et al,[30] 2017	United States	≥45 d	Cohort quartiles	National sample of CoC-accredited hospitals	4868	1998–2011	≥45 d: 25	OC: 100	Unspecified I: 39 II: 22 III: 10 IV: 29	S: 70 S + RT: 20 S + CRT: 10	OS ≤30 d, 1 [Ref] 30–45 d, NR ≥45 d, 0.98 (0.88–1.09)	12
Tsai et al,[31] 2017	Taiwan	>120 d	Not specified	Population-based cancer registry	21 263	2004–2010	>120 d: 3	OC: 100	Unspecified I: 28 II: 20 III: 12 IV: 40	S: 93 RT: 5 chemotherapy: 2	OS <30 d, 1 [Ref] 31–120 d, 1.18 (1.11–1.25) ≥120 d, 1.32 (1.19–1.47)	12
Liao et al,[32] 2017	Taiwan	1: >30 d 2: >20 d	1: Calendar-based (mo) 2: RPA	Population-based cancer registry	18 677	2004–2010	1: >30 d: 19 2: >20 d: 43	OC: 100	Clinical I: 18 II: 37 III: 10 IV: 26	S: 93 (C)RT: 7	OS (calendar-based) ≤30 d, 1 [Ref] 31–60 d, 1.10 (1.03–1.18) 61–90 d, 1.26 (1.08–1.46) ≥91 d, 1.26 (1.12–1.41) OS (RPA) ≤20 d, 1 [Ref] 21–45 d, 1.07 (1.02–1.13) 46–90 d, 1.25 (1.14–1.38) ≥91 d, 1.28 (1.14–1.45)	12
Polesel et al,[33] 2017	Italy	>45 d	Not specified	Population-based cancer registry	1616	2003–2009	>45 d, 25	OC: 29 OP: 21 HP: 13 Lx: 37	Unspecified I: 18 II: 7 III: 6 IV: 26 Unk: 43	S: 37 RT: 10 CRT: 30 IC + RT: 23	OS ≤30 d, 1 [Ref] 31–44 d, 1.08 (0.90–1.30) 45–89 d, 1.13 (0.92–1.39) ≥90 d, 1.47 (1.05–2.05)	13
Murphy et al,[10] 2016	United States	1: >60 d 2: >67 d	1.: Calendar-based (mo) 2: RPA	National sample of CoC-accredited hospitals	51655	2003–2005	1: >60 d, 10 2: >67 d, NR	OC: 29 OP: 22 HP: 7 Lx: 42	Clinical I: 24 II: 16 III: 21 IV: 39	S: 19 S + RT: 17 S + CRT: 11 RT: 23 CRT: 31	OS (calendar-based) ≤30 d, 1 [Ref] 31–60 d, 0.99 (0.96–1.02) 61–90 d, 1.08 (1.03–1.13) ≥91 d, 1.23 (1.15–1.32) Median OS (RPA) ≤46–52 d, 72 mo 53–67 d, 61 mo >67 d, 47 mo	13

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Source	Country	Definition of Delayed DTI	Derivation of Definition of Delay	Data Source	Sample Size, No.	Years of Diagnosis or Treatment	Freq of Delay, %	HN Subsite, %	AJCC Stage Grouping,%	Treatment Modality, %	Association of Delay to Survival, aHR(95%CI)	Quality Score
Sharma et al,[34] 2016	United States	>30 d	Cohort median	National sample of CoC-accredited hospitals	6606	2003–2006	>30 d: 54	OP: 100	Clinical III: 26 IV: 74	CRT: 100	OS ≤30 d, 1 [Ref] >30 d, 1.12 (1.03–1.20)	11
Chiou et al,[35] 2016	Taiwan	>21 d	Calendar-based (wk, as determined by *P* values)	Population-based cancer registry	2703	2007-not specified	>21 d: 59	OC: 100	Unspecified 0: 1 I: 21 II: 20 III: 17 IV: 41	NR	Median OS <21 d, 60.7 mo >21 d, 62.7 mo	10
Naghavi et al,[36] 2016	United States	>45 d	Not specified	Single academic medical center	1802	1998–2013	>45 d: 51	OP: 47 OC: 25 Lx: 19 HP: 5	Unspecified I: 6 II: 9 III: 18 IV: 67	S + (C)RT: 32 (C)RT: 63	OS ≤45 d, 1 [Ref] >45 d, 1.75 (1.06–2.88)	11
Van Harten et al,[37] 2015	Netherlands	>30 d	Calendar-based (wk)	National Cancer Registry	13 140	2005–2011	>30 d: 65	OC: 33 OP: 19 NP: 7 HP: 7 Lx: 28 salivary: 6	Unspecified I: 31 II: 18 III: 15 IV: 36	S: 29 S + (C)RT: 27 CRT: 44	OS 7 d, 1.07 (1.06–1.08)	13
Van Harten et al,[38] 2014	Netherlands	>30 d	Calendar-based (mo)	Single comprehensive cancer center	2493	1990–2011	>30 d: 68	OC: 27 OP: 33 HP: 11 Lx: 29	Unspecified I-II: 40 III-IV: 60	S ± (C)RT: 48 (C)RT: 52	DSS ≤30 d, 1 [Ref] >30 d, 0.91 (0.77–1.07)	12
Caudell et al,[39] 2011	United States	>51 d	Cohort quartiles	Single academic medical center	427	1995–2007	>51 d: 25	OC: 5 OP: 55 HP: 9 Lx: 21 Other: 10	Clinical III: 24 IV: 76	RT:28 CRT: 72	OS ≤24 d, 1 [Ref] 25–34 d, P = NS 35–50 d, P = NS ≥50 d, P = .47 (HR, NR) LRC ≤24 d, 1 [Ref] 25–34 d, P = NS 35–50 d, P = NS ≥50 d, P = .22 (HR, NR)	10

Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CoC, Commission on Cancer; CRT, chemoradiotherapy; DSS, disease-specific survival; Freq, Frequency; HR, hazard ratio; HP, hypopharynx; HN, head and neck; IC, induction chemotherapy; LRC, locoregional control; Lx, larynx; NP, nasopharynx; NR, not reported; NS, not significant (as reported by study authors without quantified *P* value); OC, oral cavity; OP, oropharynx; OS, overall survival; Ref, Reference; RFS, recurrence-free survival; RPA, recursive partition analysis; RT, radiotherapy; S, surgery; Unk, unknown.

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Table 2.

Surgery to Postoperative Radiotherapy (S-PORT)

Source	Country	Definition of Delayed S-PORT	Derivation of Definition of Delay	Data Source	Sample Size, No.	Years of Diagnosis or Treatment	Freq of Delay, %	HN Subsite, %	AJCC Stage Grouping, %	Treatment Modality, %	Association of Delay to Survival, aHR (95% CI)	Quality Score
Tam et al,[20] 2018	United States	>6 wk	NCCN guidelines	National sample of CoC-accredited hospitals	16 733	2005–2012	>6 wk: NR	OC: 41 OP: 42 HP: 3 Lx: 14	Pathologic I: 2 II: 4 III: 13 IV: 62 Unk: 20	S + CRT: 100	OS ≤6 wk, 1 [Ref] >6 wk, 1.10 (1.04–1.16)	13
Chen et al,[19] 2018	United States	>6 wk	NCCN guidelines	Single academic medical center	132	2008–2016	NR	OC: 100	Pathologic I: 7 II: 18 III: 12 IV: 63	S + RT: 63 S + CRT: 37	OS ≤6 wk, 1 [Ref] >6 wk, 1.34 (0.53–3.36) RFS ≤6 wk, 1 [Ref] >6 wk, 2.42 (1.13–5.21)	11
Cramer et al,[15]2017	United States	>6 wk	NCCN guidelines	National sample of CoC-accredited hospitals	35 716	2004–2014	>6 wk: 55	NR	NR	NR	OS >6 wk, 1 [Ref] ≤6 wk, 0.92 (0.89–0.96)	13
Graboyes et al,[14]2017	United States	>6 wk	NCCN guidelines	National sample of CoC-accredited hospitals	41291	2006–2014	>6 wk: 56	OC: 31.5 OP: 41.6 HP: 2.6 Lx: 24.3	Pathologic I: 7 II: 7 III: 13 IV: 44 Unk: 29	S + RT: 46 S + CRT: 53 Unk: 1	OS ≤6 wk, 1 [Ref] >6 wk, 1.13 (1.08–1.19)	13
Fujiwara et al,[30]2017	United States	>64 d	Cohort quartiles	National sample of CoC-accredited hospitals	1462	1998–2011	>64 d: 25	OC: 100	Unspecified I: 9 II: 16 III: 18 IV: 57	S + RT: 68 S + CRT: 32	OS <50 d, 1 [Ref] 50–64 d, NR ≥64 d, 0.96 (0.81–1.15)	12

Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CoC, Commission on Cancer; CRT, chemoradiotherapy; Freq, Frequency: HN, head and neck; HP, hypopharynx; Lx, larynx; NCCN, National Comprehensive Cancer Network; NR, not reported; OC, oral cavity; OP, oropharynx; OS, overall survival; Ref, Reference; RFS, recurrence-free survival; RT, radiotherapy; S, surgery; Unk, unknown.

Table 3.

Treatment Package Time (TPT)

Source	Country	Definition of Delayed TPT	Derivation of Definition of Delay	Data Source	Sample Size, No.	Years of Diagnosis or Treatment	Freq of Delay, %	HNSubsite, %	AJCC Stage Grouping, %	Treatment Modality, %	Association of Delay to Survival, aHR(95%CI)	Quality Score
Tam et al,[20] 2018	United States	1: >13 wk 2: >97 d	1: Prespecified (prior data) 2: RPA	National sample of CoC-accredited hospitals	16 733	2005–2012	1: >13 wk, 66 2: >97 d: NR	OC: 41 OP: 42 HP: 3 Lx: 14	Pathologic I: 2 II: 3 III: 13 IV: 62 Unk: 20	S + CRT: 100	OS (prespecified) ≤13 wk, 1 [Ref] >13 wk, 1.07 (1.01–1.13)[a] Median OS (RPA) ≤97 d, 10.0 y >97 d, 8.2 y	13
Guttmann et al,[18] 2018	United States	≥11 wk	Not specified	National sample of CoC-accredited hospitals	15 234	2004–2012	NR	OC: 29 OP: 55 HP: 2 Lx: 14	Pathologic III: 24 IV: 76	S + RT: 37 S + CRT: 61 Unk: 1	OS <11 wk, 1 [Ref] 11–12 wk, 1.19 (1.03–1.37) 13–15 wk, 1.36 (1.18–1.56) ≥16 wk, 1.51 (1.31–1.74)	12
Chen et al,[19] 2018	United States	>11 wk	Not specified	Single academic medical center	132	2008–2016	>11 wk: 73	OC: 100	Pathologic I: 7 II: 18 III: 12 IV: 63	S + RT: 51 S + CRT: 49	OS ≤11 wk, 1 [Ref] >11 wk, 6.68 (1.42–31.4) RFS ≤11 wk, 1 [Ref] >11 wk, 2.94 (1.20–7.18)	12
Fujiwara et al,[30] 2017	United States	≥161 d	Cohort quartiles	National sample of CoC-accredited hospitals	1462	1998–2011	≥161 d: 25	OC: 100	Unspecified I: 9 II: 16 III: 18 IV: 57	S + RT: 68 S + CRT: 32	OS ≤136 d, 1 [Ref] 136–161 d: NR ≥161 d, 0.98 (0.82–1.17)	12
Tribius et al,[40] 2016	Germany	1: ≥100 d 2: ≥87 d	1: Not specified 2: Decision tree	Single institution	272	2004–2014	1: ≥100 d, 18 2: ≥87 d, 45	OC: 27 OP: 39 HP or Lx: 16 Other: 18	Unspecified III: 35 IV: 65	S + RT: 57 S + CRT: 43	OS <100 d, 1 [Ref] ≥100 d, 4.1 (2.04–8.27) <87 d, 1 [Ref] ≥7 d, 3.3 (1.52–7.03) DFS <100 d, 1 [Ref] ≥100 d, 1.8 (0.76–4.18) <87 d, 1 [Ref] ≥87 d, 2.2 (1.04–4.59)	13

Abbreviations: aHR, adjusted hazard ratio; AJCC, American Joint Committee on Cancer; CoC, Commission on Cancer; CRT, chemoradiotherapy; DFS, disease-free survival; Freq, Frequency; HN, head and neck; HP, hypopharynx; Lx, larynx; NR, not reported; OC, oral cavity; OP, oropharynx; OS, overall survival; Ref, Reference; RFS, recurrence-free survival; RPA, recursive partitioning analysis; RT, radiotherapy; S, surgery; Unk, unknown.

[a]Discrepancy between results reported in abstract (aHR, 1.10; 95%CI, 1.04–1.17) and results and tables (aHR, 1.07; 95%CI, 1.01–1.13).