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National treatment times in oropharyngeal cancer treated with primary radiation or chemoradiation☆

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ABSTRACT

Objective: To characterize treatment delays in oropharyngeal cancer treated with radiation in a national sample, identify factors associated with delays, and associate treatment delays with survival.
Materials and Methods: We included adults in the National Cancer Database treated for oropharyngeal cancer with primary radiation or chemoradiation 2010–2013. We characterized diagnosis-to-treatment initiation, radiation treatment duration, and diagnosis-to-treatment end intervals as medians. We examined delays for association with patient, tumor, and treatment characteristics and with overall survival with multivariable logistic and Cox proportional hazards regression, respectively.
Results: 4089 patients were included; 12% received radiation alone and 88% chemoradiation. The incidence of human papilloma virus-associated tumors was 64%. Median durations of diagnosis-to-treatment initiation, radiation duration, and diagnosis-to-treatment end were 35, 50, and 87 days, respectively. Human papilloma virus-positive tumors were linked to decreased delays in radiation treatment duration and diagnosis-to-treatment end (OR = 0.72 (0.60–0.85), $p < 0.001$ and OR = 0.79 (0.66–0.95), $p = 0.010$, respectively). Delays in radiation treatment duration and diagnosis-to-treatment end were negatively associated with overall survival (HR = 1.23 (1.03–1.47), $p = 0.024$ and 1.24 (1.04–1.48), $p = 0.017$, respectively). When examined separately, radiation duration remained associated with decreased overall survival in patients with human papilloma virus-negative (HR = 1.29 (1.03–1.63), $p = 0.030$) but not human papilloma virus-positive tumors (HR = 1.17 (0.89–1.54), $p = 0.257$).
Conclusion: These median durations can serve as national benchmarks. Diagnosis-to-treatment end interval is associated with overall survival in all patients, and radiation treatment duration in patients with human papilloma virus-negative tumors. These intervals could be considered quality indicators for oropharyngeal squamous cell carcinoma treated with primary radiation or chemoradiation.

Introduction

Treatment delays in cancer care have been linked to decreased survival and local control, increased patient anxiety, and decreased perception of care [1–8]. There are a variety of causes of delays, including referral to specialists, treatment planning and scheduling, and breaks during treatment [9].

The complex and multidisciplinary nature of head and neck cancer (HNC) treatment makes patients particularly vulnerable to delays, which have been examined in HNC for decades [10,11]. Recent work suggested that time from diagnosis to treatment initiation is increasing for HNC, and that each month delay results in a 15% reduction in local control [12–14]. Data are inconsistent regarding the implications this has for survival [15,16]. Prolonged radiation treatment (RT), on the other hand, has been consistently associated with survival [17–25].

Treatment delays have been examined at many HNC subsites, but there are few studies in oropharyngeal squamous cell carcinoma (OPSCC). Those that exist are limited to single-institution cohorts and often combine OPSCC with oral cavity cancer [15,26–28] Unlike other types of HNC, most OPSCC is attributed to Human Papilloma Virus

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(HPV) infection [29–33]. There is speculation that these less aggressive tumors may be less affected by treatment delays, however this question remains unanswered [23,34]. Sharma et al. previously used the National Cancer Database (NCDB) to examine prolonged diagnosis-to-treatment initiation interval in OPSCC patients and found that prolongation was associated with decreased survival [35]. However HPV status, a strong predictor of survival, was not controlled for.

This study uses the NCDB to characterize delays in diagnosis-to-treatment initiation, RT duration, and diagnosis-to-treatment end intervals in OPSCC treated with primary radiation or chemoradiation. Specifically, we characterized the distribution of delays for the establishment of national benchmarks, identified factors predictive of delays, and associated delays with overall survival (OS) in HPV-positive and negative patients. We also included an additional cohort treated with surgery prior to RT initiation to examine the association of treatment delays with overall survival in patients treated with different modalities.

Materials and methods

Data source

The NCDB is a collaboration between the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society that details cancer treatment and outcomes of patient treated at CoC-accredited institutions across the United States, accounting for 70% of cancers diagnosed nationwide. It has been in existence since 1985 and is detailed elsewhere [36].

Patient selection

We included patients in the NCDB diagnosed with OPSCC 2010–2013 and treated with RT or concurrent chemoradiation (CCRT) (Fig. 1). Inclusion dates were chosen to select a modern cohort with adequate survival data. Patients with squamous cell carcinoma (SCC) histology were identified by ICD-O-3 codes (8051, 8070-8079, 8082-8084, 8094, and 8560). Date of diagnosis is recorded as date of histologic confirmation of diagnosis. Chemotherapy initiation more than 30 days before RT initiation was defined as neoadjuvant; this is beyond the scope of this analysis and these patients were therefore excluded. Recommended RT duration is 6–7 weeks; in order to allow slight schedule variations, RT duration less than 35 days was defined as incomplete and these patients were excluded [10]. Other exclusion criteria included treatment at a non-NCDB facility and incomplete information on staging, treatment, vital status, and HPV status. Patients with outlier values for dependent variables (more than 1.5 interquartile ranges below the first or above the third quartile) were excluded from individual analyses.

Three treatment intervals were recorded. Diagnosis-to-treatment initiation (DTI) was defined as days between diagnosis and initiation of definitive treatment, RT duration (RTD) as days from the first to the last day of RT, and diagnosis-to-treatment end (DTE) as days from diagnosis to completion of the primary course of therapy. Disease-free and disease-specific survival are not available in the NCDB therefore OS was used as the primary outcome measure.

Comorbidities in terms of the Charlson-Deyo comorbidity index were simplified to zero or more than zero [37]. Care transitions were defined as diagnosis and initial treatment at different facilities. CCRT was defined as initial treatment with both chemotherapy and radiation. Treatment location was defined as Northeast (mid-Atlantic/New England), South (South Atlantic), Central (East/West North Central and East/West South Central), or West (Mountain/Pacific). Facility volume was classified by number of OPSCC cases treated per year, defined as more than nine (high-volume) 6–9 (medium-volume) and < 6 (low-volume). Smoking status and details of chemotherapy regimen are not available.

Statistical analysis

To determine factors predictive of delays, patients in the first and second quartile (not delayed) were compared to patients in the fourth quartile (delayed) for each interval. Patient-, tumor-, and treatment-specific factors (Table 1) were examined for association with delays via chi-squared analysis. These factors were associated with delays via multivariable binary logistic regression. Delays were associated with OS via Cox proportional hazards regression, controlling for patient, tumor, and treatment factors (as above). For treatment intervals associated with OS, iterative partitioning analysis was performed to identify cut-offs at which the association of delays with OS became statistically significant.

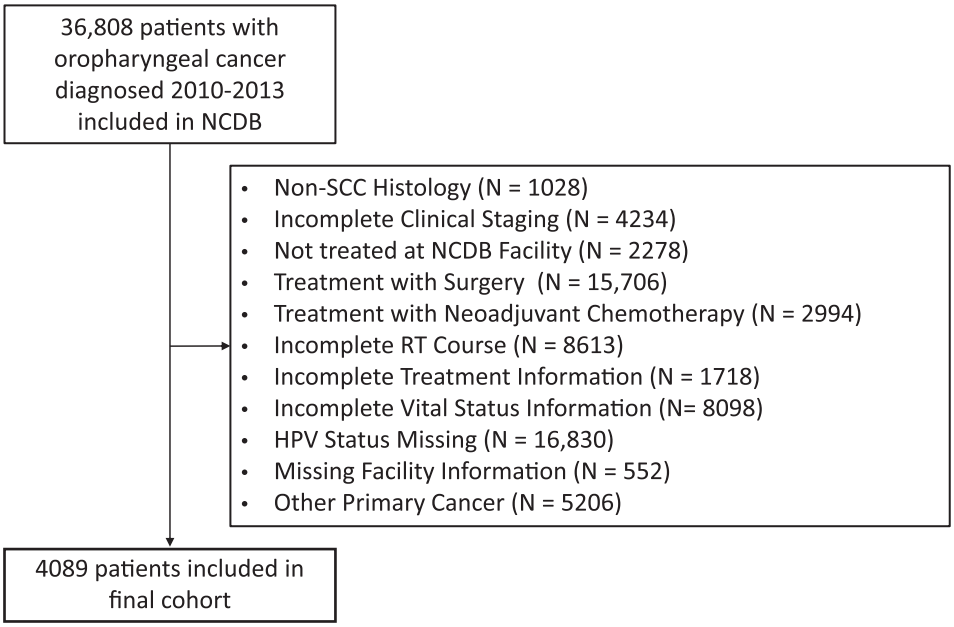

Fig. 1. Case Selection. Inclusion and exclusion criteria for the final study cohort. Numbers of patients excluded based on each criteria are shown. NCDB = National Cancer Database. SCC = Squamous Cell Carcinoma. RT = radiation treatment. HPV = Human Papilloma Virus.