Oral Oncology 79 (2018) 64–70

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Upfront surgery versus definitive chemoradiotherapy in patients with human Papillomavirus-associated oropharyngeal squamous cell cancer

Jacqueline R. Kelly[a], Henry S. Park[a], Yi An[a], Wendell G. Yarbrough[b,d], Joseph N. Contessa[a], Roy Decker[a], Saral Mehra[b], Benjamin L. Judson[b], Barbara Burtness[c], Zain Husain[a,*]

[a] Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, United States
[b] Division of Otolaryngology, Department of Surgery, Yale School of Medicine, New Haven, CT, United States
[c] Department of Medical Oncology, Yale School of Medicine, New Haven, CT, United States
[d] Department of Pathology, Yale School of Medicine, New Haven, CT, United States

ARTICLE INFO

Keywords:
Oral cancer
Human papillomavirus
Oropharynx
Squamous cell cancer
Radiotherapy
Surgery
Neoplasm

ABSTRACT

Objectives: Currently, human papillomavirus-associated oropharyngeal squamous cell carcinoma (HPV-A OPC) is managed with either primary surgery or definitive chemoradiotherapy (CRT), despite the lack of supporting randomized prospective data. We therefore assessed the outcomes of each treatment strategy using the National Cancer Database (NCDB).

Methods: The NCDB was used to identify patients diagnosed with cT1 N2a-2b or cT2 N1-2b HPV-A OPC from 2010 to 2013 who underwent treatment with primary surgery or CRT. Demographic and clinicopathologic predictors of treatment were analyzed by the chi-square test and logistic regression. Overall survival (OS) was evaluated using multivariable Cox proportional hazard regression, Kaplan-Meier, log-rank test, and propensity score-matched analysis.

Results: We identified 3063 patients; 1576 (51.5%) received CRT and 1487 (48.5%) underwent primary surgery. Median follow up was 32 months. 972 (65.4%) surgical patients received adjuvant CRT. On multivariable Cox regression, 3-year OS was comparable between surgery and CRT (hazard ratio [HR] 1.08, 95% confidence interval [CI] 0.83–1.41, $P = 0.58$). Inferior OS was significantly associated with increasing clinical T and N stage, older age, and non-private insurance. Propensity score-matching yielded a 2526 patient cohort and redemonstrated similar OS (HR, 1.09; 95% CI 0.81–1.47; $P = 0.55$). Comparable outcomes persisted in a subset analysis of patients with margin-negative resection, with 3-year OS 90.8% in CRT patients vs. 93.6% in surgery patients (log-rank $P = 0.27$).

Conclusions: Upfront surgery and CRT yielded comparable 3-year OS outcomes in this cohort. In this national sample, 65.4% of surgical patients received trimodal therapy with adjuvant CRT, highlighting the need for improved patient selection for primary surgery.

Introduction

Human papillomavirus-associated oropharyngeal squamous cell cancer (HPV-A OPC) incidence has increased significantly over the past two decades, accounting for over 70% of newly diagnosed OPC and now having an incidence higher than that of uterine cervical cancer [1,2]. HPV-A and HPV-negative OPCs are now considered distinct diseases, as evidenced by different etiologies, natural histories [3,4], biomolecular signatures [5–7], treatment responsiveness [8], and staging systems [9]. Numerous prospective trials have demonstrated that HPV positivity confers improved prognosis compared to patients with similar stage HPV-negative tumors [8,10–17].

The current standard of care for locally advanced HPV-A OPC consists of definitive concurrent chemoradiation (CRT) or primary surgery with or without adjuvant radiation (RT) or CRT. While effective, conventional management incurs long-term morbidity that escalates with treatment intensity and significantly impairs quality of life [18], possibly representing overtreatment in this favorable-prognosis patient population. In response, the role of surgery is expanding [19], including the use of minimally invasive approaches such as transoral robotic surgery (TORS) [20,21], with the goal of minimizing adjuvant therapy and treatment morbidity. While the rate of major complications with TORS is decreasing with higher surgeon case volume [22], concern for treatment-induced morbidity has prompted the initiation of

* Corresponding author at: Smilow Cancer Hospital, Yale Cancer Center, P.O. Box 208040, New Haven, CT 06510, United States.
E-mail address: Zain.husain@yale.edu (Z. Husain).

https://doi.org/10.1016/j.oraloncology.2018.02.017
Received 14 November 2017; Received in revised form 12 February 2018; Accepted 21 February 2018

multiple trials aiming to reduce treatment-related toxicity in this population via reduction of adjuvant therapy or the use of less toxic definitive CRT regimens.

Nonetheless, a prospective, randomized trial comparing oncologic outcomes between primary surgery and definitive CRT in this patient population has not been conducted to date. In the absence of randomized prospective data, carefully controlled population-based analyses can provide crucial evidence regarding comparative effectiveness. We therefore used the National Cancer Data Base (NCDB) to characterize the patterns of care and the effectiveness of primary surgery vs. definitive CRT among patients with cT1 N2a-2b or cT2 N1-2b HPV-A OPC.

Methods

Data source

The NCDB is a combined program of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. There are more than 1500 CoC–accredited institutions, and the NCDB includes more than 70% of patients newly diagnosed with cancer in the United States [23].

Study sample

The institutional review board of Yale University granted this study exempt status and waived requirement for consent. Using the NCDB, we identified patients who would likely be eligible for transoral surgery or CRT based on receiving a diagnosis of cT1 N2a-2b or cT2 N1-2b HPV-A OPC between 2010 and 2013 (Fig. 1). HPV status was derived by recording the results of any HPV testing performed on pathologic specimens from the primary tumor or a metastatic site. We defined HPV positivity as patients who tested positive for high-risk HPV. The time period of 2010–2013 was selected as HPV status was not coded for patients diagnosed before 2010 and adequate follow up data was not available for patients diagnosed after 2013. Patients recommended to receive RT alone per NCCN guidelines were excluded, as they have earlier stage disease and/or more favorable disease characteristics that may skew outcomes results in favor of the nonsurgical group. CRT was defined as chemotherapy initiation within 14 days of RT initiation. CRT patients that fell outside of this window were excluded, as their treatment was no longer considered concurrent. Surgery was defined as surgical excision of the primary tumor site, excluding codes for local tumor destruction and local tumor excision to eliminate patients undergoing excisional biopsy only.

Statistical methods

Patient clinicodemographic factors were categorized and compared by treatment group (primary surgery vs. CRT) using the chi-square test. A multivariable logistic regression model was constructed using backward elimination with a univariable inclusion criterion of $P < 0.10$. The variance inflation factor was estimated to exclude the possibility of overlapping of highly correlated independent variables, and goodness-of-fit was ensured using the Hosmer-Lemeshow test.

OS was evaluated using the time from diagnosis until death or the date the patient was last contacted. Median follow up time was calculated using the reverse Kaplan-Meier method [24]. Univariable Cox regression was used to calculate unadjusted hazard ratios (HR) for survival using clinicopathologic factors potentially affecting survival. Variables trending towards significance on univariable analysis ($P < 0.10$) were included in a Cox multivariable regression to identify factors significantly associated with improved OS. Schoenfeld residuals were calculated to ensure the proportional hazards assumption was not violated. The Kaplan-Meier estimator and the log-rank test were used to compare OS between treatment groups. Shared frailty analysis was performed to examine heterogeneity between treatment centers.

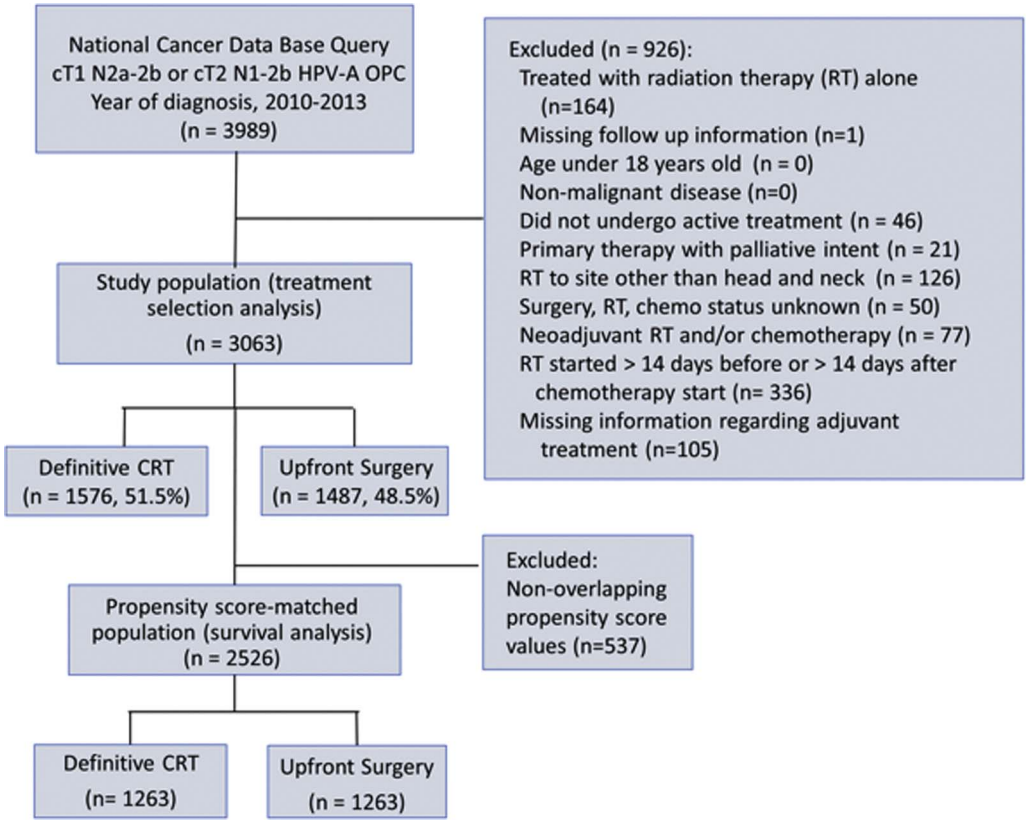

Fig. 1. Identification of Study Cohort.