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Comparative effectiveness of induction chemotherapy for oropharyngeal squamous cell carcinoma: A population-based analysis

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SUMMARY

Objectives: Despite several randomized trials, the optimal chemotherapy paradigm for locally advanced oropharyngeal carcinoma (OPSCC) is controversial. This population-based analysis assessed the overall survival (OS) benefit of induction chemotherapy (IC) for patients with stage III–IVB OPSCC.
Materials and Methods: Patients in the National Cancer Database with stage III–IVA-B OPSCC treated with curative-dose radiotherapy and IC or concurrent chemotherapy (CRT) between 2003 and 2011 were eligible. The primary outcome was OS, and secondary endpoints included OS for high-risk (T4 and/or N3 disease) and human papillomavirus (HPV) subsets.
Results: Of the 14,856 analyzed patients, 78% and 22% received CRT and IC, respectively. With a median follow-up for surviving patients of 44 months, the 5-year OS probability for the entire cohort was 66% (66% CRT vs. 64% IC, $p = 0.022$). Multivariable survival analysis showed no significant difference between CRT and IC (hazard ratio, HR, 0.95 for IC, $p = 0.255$), and sensitivity analyses to adjust for immortal time bias brought the HR to 1.0 ($p = 0.859$). There was also no OS difference for high-risk patients. There was a trend in favor of CRT for HPV-positive OPSCC (HR 1.63 with IC, $p = 0.064$), with a significant OS benefit for HPV-negative, high-risk OPSCC (HR 0.63, $p = 0.048$).
Conclusion: For the vast majority of patients, including HPV-positive individuals, there was no difference in OS with IC, arguing for CRT to remain as the standard therapy. Subset analysis revealed a small cohort of aggressive cancer (T4/N3 HPV-negative) which may benefit from from IC, although selection bias could not be ruled out.

Introduction

The optimal non-surgical treatment for locally advanced oropharyngeal squamous cell carcinoma (OPSCC) is frequently contested [1]. Although definitive chemoradiotherapy (CRT) has largely become the standard-of-care, several older randomized trials suggested that induction chemotherapy (IC) improves survival over radiotherapy (RT) alone [2,3], and IC proponents further point to high response rates with modern regimens [4] and a significant reduction in distant metastasis risk to support initial treatment with chemotherapy [5]. Critics of IC contend that this paradigm is associated with increased toxicity that may impact successful completion of definitive radiotherapy and point to three negative randomized trials comparing definitive CRT with docetaxel-based IC followed by CRT, also termed sequential therapy.

Although these latter studies included all subsites of head and neck cancer, OPSCC was the most common in each of them. The randomized PARADIGM trial evaluated 3 cycles of docetaxel–cisplatin–fluorouracil (DPF) followed by risk-adapted CRT with CRT alone, finding no significant difference in overall survival, although it closed early to accrual [6]. The contemporaneous and larger DeCIDE study randomized patients between 2 cycles of DPF followed by hyperfractionated CRT and CRT alone, also finding no significant difference in OS, although the cumulative risk of metastasis was roughly halved in the induction arm [7]. Finally, the Spanish Head and Neck Cooperative Group randomized 439

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patients between DPF followed by CRT, PF followed by CRT, and CRT alone, also finding no significant differences in survival [8]. The relatively favorable outcomes in the American trials, in particular, have led to the concern that the improved prognosis of human papillomavirus (HPV)-driven cancers eliminated any marginal benefit from intensified therapy. An additional argument provoked by these trials is that strictly reducing the risk of metastasis with IC is unlikely to lead to a significant survival advantage, given a relatively low absolute risk of distant metastasis as first failure and the competing risks of locoregional failure and treatment-related mortality [9].

Despite these negative studies, IC remains an often-implemented paradigm in head and neck cancer [10], and in fact, a 1996 patterns-of-care study of non-academic physicians suggested that induction chemotherapy was implemented in over half of all patients with locally advanced head and neck cancer [11]. It is still a level 3 treatment option in the NCCN Guidelines for OPSCC [12]. Although randomized trials are the foundation of clinical decision-making, comparative effectiveness studies may provide additional insight into comparisons between IC and CRT by characterizing real-world outcomes using many thousands of patients. In this study, we have performed a comparative effectiveness study of IC versus CRT for stage III–IVB OPSCC using the National Cancer Database.

Methods

Database

The National Cancer Database is a combined program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. There are over 1500 CoC-accredited institutions, and the NCDB includes over 70% of patients newly diagnosed with cancer [13]. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or our conclusions drawn from these data.

Cohort definition

Eligible patients were diagnosed with pathologic stage III–IVB oropharyngeal squamous cell carcinoma between 2003 and 2011. All patients were required to initiate treatment within 4 months of diagnosis. For the primary analysis, we aimed to tightly define the two cohorts to ensure a treatment approach that aligned as closely as possible with the pre-determined treatment arms. Thus, IC was defined as the delivery of 2 or more chemotherapy agents delivered 21 days or more before the start of RT. Chemoradiotherapy was defined as the delivery of chemotherapy within 1 week of the start of RT. For both treatment groups, the total RT dose was mandated between 66 and 75.6 Gray (Gy). Patients did not undergo surgery before chemotherapy and radiotherapy initiation.

Determination of predictor variables

Predictors were divided into clinical, geographic, socioeconomic, and institutional variables. Several of the ordinal variables were categorized by the NCDB, as quartiles relative to the US population, and age, distance from the facility, and yearly patient volume were stratified into quartiles. Patient volume was also dichotomized into the upper decile versus lower 90%. Human papillomavirus status was recorded in years 2010 and 2011, and patients were considered HPV positive if HPV16 and/or HPV18 were found.

Outcome variables and accounting for immortal time bias

The primary endpoint of this retrospective study was overall survival (OS), defined from the date of diagnosis. However, because IC patients did well enough during chemotherapy to then receive full-dose RT, this primary analysis suffers from immortal time bias in favor of IC [14]. In other words, patients who did not tolerate or survive IC were excluded from the analysis, and so their survival results were artificially higher. In order to account for this bias, we performed two subset analyses. First, we re-defined survival from the start of radiotherapy, so time zero starts at the same effective time in the therapy. Second, we performed a landmark analysis at six months, so that only patients who have survived a minimum of 6 months from diagnosis were included.

Statistical analyses

Differences in patient characteristics between patients who received IC or CRT were tested using the chi-squared test. Because the aim of this analysis was to study OS between IC and CRT and successful delivery of therapy was required for inclusion, we did not further investigate predictors of treatment paradigm. Univariable survival analyses were performed with the log-rank test. Multivariable survival analysis was then performed using stepwise selection, with all covariates included in the initial regression and preservation in the model if the adjusted p value was 0.05 or less.

We made the *a priori* hypothesis based on influential retrospective data that patients with T4 and/or N3 disease (termed "high-risk") would be most likely to benefit from systemically-active chemotherapy, since these patients have the highest risk of metastasis [15]. Thus, we performed a subset analysis in which the regression was limited to patients with T4 and/or N3 disease. Secondly, we performed a second subset analysis in patients who were known HPV-negative and HPV-positive, since this well-recognized etiologic and prognostic factor may inform the relative benefit of IC. Because the population of patients with known HPV subsets was small, we also developed individual propensity-matched cohorts for those who were HPV-positive and negative. This one-to-one propensity matching was then carried out using the caliper match algorithm described by Coca-Perraillon [16], with the caliper width set to 0.05, and these cohorts were compared using a log-rank test, and the hazard ratio (HR) was derived using univariable Cox regression. All analyses were performed with SAS 9.4 (Cary, NC).

Results

Patient and treatment characteristics

Patient and treatment characteristics are shown in Table 1. The cohort was predominantly white, male and relatively young. Twenty-six percent of the population presented with T4 and/or N3 disease. Only a small number of patients had known HPV status, and the majority of these individuals were HPV-positive. Patients treated with IC had more locoregionally advanced disease, with a higher percentage of T4 and N3 cancers. The socioeconomic variables were favorable, and the majority of patients carried private insurance. Fewer than 10% of patients were treated at a community cancer program, with most treated at a Comprehensive Community Cancer Program.

The mean numbers of elapsed days of radiotherapy were 62.7 and 67.6 for CRT and IC, respectively (t-test $p = 0.011$). The median numbers of elapsed days of radiotherapy were 51 for the entire