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Original research article

A comparison of concurrent cisplatin versus cetuximab with radiotherapy in locally-advanced head and neck cancer: A bi-institutional analysis

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ABSTRACT

Aim: To present our experience comparing cisplatin- and cetuximab-based radiotherapy for locally-advanced head and neck squamous cell carcinoma.

Background: The comparative effectiveness of cisplatin-based chemoradiotherapy (CRT) versus cetuximab-based bioradiotherapy (BRT) for locally-advanced head and neck squamous cell carcinoma (LAHNSCC) continues to be explored.

Materials and methods: Outcomes of LAHNSCC patients treated with CRT (125) or BRT (34) at two institutions were compared retrospectively, with attention to overall survival (OS), cancer-specific survival (CSS), locoregional control (LRC), and distant control (DC). Univariate analysis (UVA) using Cox regression was performed to explore the association of intervention with survival and disease control, and multivariate (MVA) Cox regression was then performed to assess the association of intervention with survival.

Results: There were significant baseline differences between the CRT and BRT groups with respect to age, race, performance status, N-classification, tobacco history, and human papillomavirus status. UVA demonstrated inferiority of BRT versus CRT with respect to both OS (hazard ratio [HR] 2.19, 95% confidence interval [95%CI] 1.03–4.63, $p = 0.04$) and CSS (HR 3.33, 95%CI 1.42–7.78, $p < 0.01$), but non-significantly different outcomes in LRC (HR 0.99, 95%CI 0.37–2.61, $p = 0.98$) and DC (HR 2.01, 95%CI 0.78–5.37, $p = 0.14$). On MVA, there was no significant OS difference between interventions (HR 1.19, 95%CI 0.42–3.35, $p = 0.74$); there were too few events for the other outcomes to draw meaningful conclusions with MVA.

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Conclusions: In our retrospective analysis, patients undergoing CRT experienced improved OS and CSS over those receiving BRT; however, disease control did not significantly differ. These findings may inform management of LAHNSCC patients.

1. Background

Among the most significant paradigm shifts in the management of locally-advanced head and neck squamous cell carcinoma (LAHNSCC) is the emergence of an organ-preservation strategy that utilizes radiotherapy (RT) as principal therapy and attempts to forgo surgery.[1–4] The improvements in disease control and survival with the addition of platinum-based cytotoxic chemotherapy to RT constitutes another.[5] Despite meaningfully improving oncologic outcomes, this combination approach entails considerable toxicity[6] and may complicate adherence to the intended treatment regimen, with potential adverse consequences for disease control and survival.[7–9] This has prompted a search for regimens offering comparable outcomes to chemoradiotherapy while simultaneously reducing toxicity.

An alternative emerged with the 2006 publication of the "Bonner trial", which demonstrated acceptable oncologic outcomes when cetuximab, an anti-epidermal growth factor receptor antibody, was combined with RT, without any reported increase in toxicity over RT alone.[10,11] While cisplatin-based chemoradiotherapy (CRT) and cetuximab-based bioradiotherapy (BRT) have subsequently proven to be the most popular regimens for LAHNSCC,[12] their comparative effectiveness continues to be debated. In a recent randomized trial, the addition of cetuximab to CRT offered no survival or local control benefit but did exacerbate acute toxicity.[13]

To date, the available randomized evidence comparing CRT to BRT consists of a single phase II trial which demonstrated no difference between the two arms in survival or disease control but was discontinued early due to slow enrollment, limiting its statistical power.[14] While the results of additional randomized trials are eagerly anticipated,[15–17] the findings from retrospective series may be informative and guide management. We therefore present our bi-institutional experience of LAHNSCC treated with CRT versus BRT.

2. Material and methods

We identified 248 patients with AJCC Stage III-IVB squamous cell carcinoma of the oropharynx or larynx diagnosed between 2004 and 2015 that were treated with radiation to at least 60 Gray and either concurrent cisplatin or cetuximab at the University of Colorado and the University of New Mexico. After excluding 43 patients undergoing induction chemotherapy and 46 receiving chemoradiotherapy in the postoperative setting, we were left with 125 CRT patients and 34 BRT patients receiving definitive radiation with systemic therapy. Generally at both institutions, cisplatin was the preferred radiosensitizer, while cetuximab was reserved for those patients whose comorbidities rendered them cisplatin-ineligible. Among CRT patients, the regimen of choice was cisplatin 100 mg/m^2 every three weeks for a total of three doses, while BRT patients typically received cetuximab according to the schedule used in the Bonner trial, with a loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly with RT.[10]

Relevant sociodemographic and tumor-related characteristics of interest were selected a priori, including age at diagnosis, gender, race, Karnofsky Performance Status,[18] AJCC T- and N-classification, tobacco use (as previously categorized[19]), human papillomavirus (HPV) status (either in situ hybridization for HPV DNA or immunohistochemistry for p16 overexpression), and primary site (oropharynx *vs.* larynx).

The primary endpoints were overall survival (OS), defined as time from LAHNSCC diagnosis to death of any cause; cancer-specific survival (CSS), defined as time from diagnosis to cancer-related death; locoregional control (LRC), defined as time from completion of RT to locoregional recurrence; and distant control (DC), defined as time from completion of RT to development of metastatic disease.

Statistical analyses were performed using SPSS V24.0 (SPSS Inc., Chicago, IL). Pearson chi-square tests were used to assess associations between variables and outcomes. Endpoints were examined using the Kaplan–Meier method, and groups were compared with the log-rank test. Cox proportional hazards regression was used to determine hazard ratios (HR) for each endpoint, with HR > 1 corresponding to increased risk for the specified event. All tests were two-sided with a $p \leq 0.05$ level of significance. The Hosmer–Lemeshow test was used to check for the goodness-of-fit of regression models.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008. This work was approved by the appropriate institutional review committees of both institutions.

3. Results

3.1. *Population characteristics*

Median follow-up for our cohort was 27.2 months. Significant baseline differences were noted between treatment groups, with BRT patients more likely to have older age, non-white race, lower KPS, less-advanced nodal disease, significant tobacco use history, and HPV-negative disease (all $p \leq 0.02$) (Table 1). No significant differences in RT administration were

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