Oral Oncology 80 (2018) 16–22

Contents lists available at ScienceDirect

Oral Oncology

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

Definitive chemoradiation for locally-advanced oral cavity cancer: A 20-year experience

Corey C. Foster[a,1], James M. Melotek[a,1], Ryan J. Brisson[b], Tanguy Y. Seiwert[c], Ezra E.W. Cohen[d], Kerstin M. Stenson[e], Elizabeth A. Blair[f], Louis Portugal[f], Zhen Gooi[f], Nishant Agrawal[f], Everett E. Vokes[c], Daniel J. Haraf[a,*]

[a] Department of Radiation and Cellular Oncology, University of Chicago, 5758 S. Maryland Avenue, M/C 9006, Chicago, IL 60637, USA
[b] Oakland University William Beaumont School of Medicine, 586 Pioneer Drive, Rochester, MI 48309, USA
[c] Department of Medicine and Comprehensive Cancer Center, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA
[d] Moores Cancer Center, University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92093, USA
[e] Department of Otolaryngology, Rush University, 1611 W. Harrison Street, Suite 550, Chicago, IL 60612, USA
[f] Department of Otolaryngology, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA

ARTICLE INFO

Keywords:
Head and neck neoplasms
Tongue neoplasms
Chemoradiotherapy
Osteoradionecrosis
Neoplasms
Squamous cell

ABSTRACT

Objectives: Definitive chemoradiation (CRT) for oral cavity squamous cell carcinoma (OC-SCC) is often criticized for poor efficacy or toxicity. We describe a favorable 20-year experience of primary CRT for locally-advanced OC-SCC.

Materials and Methods: Patients with locally-advanced, stage III/IV OC-SCC receiving primary concomitant CRT on protocols from 1994 to 2014 were analyzed. Chemotherapy included fluorouracil and hydroxyurea with other third agents. Radiotherapy (RT) was delivered once or twice daily to a maximum dose of 70–75 Gy. Intensity-modulated RT (IMRT) was exclusively used after 2004. Progression-free survival (PFS), overall survival (OS), locoregional control (LRC), and distant control (DC) were calculated by the Kaplan-Meier method and compared across treatment decades using the log-rank test. Rates of osteoradionecrosis (ORN) requiring surgery were compared across treatment decades using the Chi-square test.

Results: 140 patients with locally-advanced OC-SCC were treated with definitive CRT. Of these, 75.7% had T3/T4 disease, 68.6% had ≥N2 nodal disease, and 91.4% had stage IV disease. Most common primary sites were oral tongue (47.9%) and floor of mouth (24.3%). Median follow-up was 5.7 years. Five-year OS, PFS, LRC, and DC were 63.2%, 58.7%, 78.6%, and 87.2%, respectively. Rates of ORN and long-term feeding tube dependence were 20.7% and 10.0%, respectively. Differences in LRC ($P = 0.90$), DC ($P = 0.24$), PFS ($P = 0.38$), OS ($P = 0.10$), or ORN ($P = 0.38$) were not significant across treatment decades.

Conclusion: Definitive CRT is a viable and feasible strategy for organ preservation for patients with locally-advanced OC-SCC.

Introduction

An estimated 32,670 new cases of oral cavity carcinoma will be diagnosed in the United States in 2017, and an estimated 6650 patients will die from this disease [1]. Thus, oral cancer remains a significant cause of morbidity and mortality despite decreasing rates of tobacco use, and oral cavity squamous cell carcinoma (OC-SCC) is the most common histologic diagnosis. While tobacco abuse is the strongest risk factor for the development of OC-SCC, concomitant alcohol consumption may synergistically increase risk [2]. Moreover, the incidence of OC-SCC without typical risk factors appears to be increasing in the United States [3]. The management of OC-SCC has generally relied upon surgical resection as the mainstay of treatment, and outcomes have remained stable over the past two decades with 5-year overall survival (OS) of approximately 60% for all comers and 33–54% for patients with locally-advanced disease [4,5].

Abbreviations: OC-SCC, oral cavity squamous cell carcinoma; OS, overall survival; RT, radiation; ORN, osteoradionecrosis; CRT, chemoradiation; IMRT, intensity-modulated radiation therapy; PFS, progression-free survival; SPSS, swallowing status performance scale; LRC, locoregional control; DC, distant control; HR, hazard ratio; CI, confidence interval; NCDB, National Cancer Database

* Corresponding author at: Department of Radiation and Cellular Oncology, The University of Chicago Medicine, 5758 S. Maryland Ave., MC 9006, Chicago, IL 60637, USA.
E-mail address: dharaf@radonc.uchicago.edu (D.J. Haraf).

[1] These authors contributed equally and should be considered as co-first authors.

https://doi.org/10.1016/j.oraloncology.2018.03.008
Received 26 January 2018; Received in revised form 14 February 2018; Accepted 12 March 2018

Management of primary tumors involving the oral tongue has been particularly challenging with inferior rates of cause-specific survival stage-for-stage compared to other oral cavity subsites as well as other disease sites within the head and neck [6]. Additionally, given the proximity to the mandible, the delivery of high-dose radiation (RT) for definitive treatment has been associated with the development of osteoradionecrosis (ORN) of the mandible due to damage to the vascular supply [7,8]. While the use of RT or definitive chemoradiation (CRT) as a strategy for organ preservation has gained traction in other subsites of the head and neck [9,10], the use of definitive CRT for OC-SCC has been tempered by concerns regarding poor efficacy or unacceptable toxicity [11–17].

Over the past two decades at the University of Chicago, we have adopted a paradigm of upfront organ function preservation using definitive CRT for locally-advanced OC-SCC with surgery reserved for salvage as necessary [18–20]. Similar to findings from trials investigating larynx preservation, we hypothesized that definitive CRT would afford a high rate of cancer control and organ preservation with acceptable treatment-related toxicity. As such, patients with locally-advanced OC-SCC were consistently offered enrollment on our prospective institutional protocols investigating primary concomitant CRT. Herein, the updated results of our experience with routine organ preservation for locally-advanced OC-SCC are presented.

Materials and Methods

Eligibility

We conducted a review of all patients with OC-SCC treated at the University of Chicago on a series of prospective trials from 1994 to 2014. The institutional protocols included in the present analysis have been previously described [18–21]. All patients had locally-advanced, stage III-IV disease. All patients were treated by a multidisciplinary team, including medical oncology, radiation oncology, and surgical oncology. Pre-treatment evaluation included history and physical as well as radiographic assessment of the primary tumor, neck, and chest. Patients were routinely referred for pre-treatment dental evaluation. Panendoscopy was performed at the discretion of the treating physician. All patients received CRT. Patients with a prior history of head and neck RT were excluded. Patients signed institutional review-board approved informed consent before initiation of therapy.

Treatment

The majority of treatments were delivered on the FHX platform consisting of concurrent 5-FU (600–800 mg/m^2/day continuous IV days 0–5), hydroxyurea (500–1000 mg PO BID days 0–5), and either once-daily (2 Gy/fraction) or twice-daily RT (1.5 Gy/fraction separated by at least 6 h on days 1–5) with 14-day cycles repeated 5–7 times. Taxane and platinum-based induction chemotherapy was delivered prior to CRT on several trials and lasted for a period of 6–8 weeks. Additional third agents in combination with the FHX platform have included paclitaxel, docetaxel, cisplatin, or cetuximab [18–21].

Intensity-modulated radiation therapy (IMRT) was adopted towards the end of the first decade of the analyzed cohort and exclusively used in the second decade. Gross disease was targeted to a dose of 70–75 Gy. Doses to low- and high-risk microscopic disease varied over the years, but were generally 50 Gy and 60 Gy, respectively, with once-daily RT and 39 Gy and 54 Gy, respectively, with twice-daily RT. The dose to the spinal cord was constrained to 45 Gy in all cases.

Physical examination and surveillance imaging were routinely performed approximately one month after completion of CRT, every 3–6 months during the first two years of follow-up, and every 6 months during years 3–5 post-treatment. During the first decade of treatment, post-CRT neck dissection was routinely performed for patients with N2-N3 neck disease; however, in the second decade, post-CRT neck dissection was generally triggered by any radiographically- or clinically-detected large or focally-abnormal lymph node.

Endpoints

OS was calculated from the time of enrollment until death from any cause. Surviving patients were censored as of the last known follow-up. Progression-free survival (PFS) was calculated from the time of enrollment until disease progression or death from any cause. Surviving patients without disease progression were censored as of the last negative exam. Time to locoregional failure was calculated as the time from enrollment until the development of locoregional recurrence, as documented on clinical exam or imaging. Time to distant failure was calculated as the time from enrollment until the development of distant metastasis detected on exam or imaging. For both time to locoregional and distant failure, patients were censored as of the last negative exam. ORN was defined as symptomatic exposure of bone requiring surgery. Dysphagia was assessed with the Swallowing Performance Status Scale (SPSS) score which is a global assessment of swallowing function assigned by a speech therapist based upon review of a video fluoroscopic oropharyngeal motility study with scores ranging from 1 (normal) to 7 (severe impairment) [18]. Scores ≥ 6 indicate requirement of enteral feeding support.

Statistical analysis

Using the intention-to-treat concept, all enrolled patients were included in statistical analyses. Survival and control rates were estimated by the Kaplan-Meier method and compared between groups using the log-rank test. Univariate Cox proportional hazards regression models were fitted to assess the effects of covariates on survival including demographic, tumor, and treatment characteristics Significant predictors on univariate analysis ($P < 0.1$) were then included in multivariate Cox proportional hazards regression models. Toxicity rates were tabulated and compared between groups using the Chi-square test. Univariate logistic regression was also conducted to assess the effects of covariates on the development of ORN including demographic, tumor, and treatment characteristics. All statistics were performed using JMP Statistical Software (v 13.0, SAS Institute, Cary, NC).

Results

Patient characteristics

From 1994 to 2014, 140 patients with previously-untreated, locally-advanced OC-SCC were treated on 12 prospective institutional protocols. Baseline characteristics are presented in Table 1. The majority of patients (91.4%) had stage IV disease. Oral tongue was the most commonly involved subsite (47.9%), followed by floor of mouth (24.3%). The majority of patients (75.7%) had T3/T4 disease. Additionally, the majority of patients had multiple or bilateral nodal involvement, with 30.0% having N2b disease and 25.7% having N2c disease.

Efficacy

The median follow-up for all patients was 5.7 years. Twenty-four patients experienced locoregional failure, which was the most common cause of disease progression. The majority of these patients (17/24–70.8%) died of their disease. Eleven patients underwent surgical salvage after locoregional failure, with four patients achieving successful long-term disease control. The remaining patients experienced either persistent locoregional failure (4/10), death due to distant disease (1/10), or death due to comorbidity (2/10).

Kaplan-Meier curves for OS and PFS for the entire cohort and for patients with T3/T4 disease are shown in Figs. 1 and 2, respectively, with numbers at risk for all Kaplan-Meier curves available in