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Induction chemotherapy followed by concurrent chemoradiation versus concurrent chemoradiation alone in the definitive management of p16-positive oropharyngeal squamous cell carcinoma with low-neck or N3 disease

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ABSTRACT

Objective: The addition of induction chemotherapy (ICT) to concurrent chemoradiation (CCRT) has been investigated as a method of improving outcomes among patients with locally advanced head and neck squamous cell carcinoma. Previous studies have consisted of heterogeneous populations with both p16-positive and p16-negative disease and varying extent of nodal disease burden. We evaluated the role of ICT in p16-positive oropharyngeal squamous cell carcinoma (OPSCC) at high-risk of distant failure.

Materials and methods: A retrospective review was conducted of 88 consecutive patients with p16-positive OPSCC with low-neck and/or N3 lymphadenopathy. Among these patients, 44 received ICT followed by CCRT, and 44 received CCRT alone with concurrent agents including Cisplatin, Carboplatin, and Cetuximab. Disease control and survival outcomes were reported after adjusting for age, T stage, N stage, and smoking status.

Results: Median follow-up for surviving patients was 47 (range: 13–115) months. Patients who received CCRT alone were older than those who received ICT (61 years vs. 56 years; p = 0.02); the groups were otherwise similarly balanced. 3-year distant metastasis: 38% vs. 18% (adjusted hazard ratio (HR) = 0.32 [0.13–0.82]; p = 0.02). 3-year progression-free survival: 49% vs. 74% (adjusted HR = 0.46 [0.22–0.93]; p = 0.03). 3-year overall survival: 67% vs. 83% (adjusted HR = 0.48 [0.21–1.12]; p = 0.09).

Conclusion: Among patients with p16-positive OPSCC with low-neck and/or N3 lymphadenopathy, ICT followed by CCRT may reduce the risk for distant failure over CCRT alone and lead to improved progression-free survival. Future trials should concentrate on patients at the highest risk of distant metastasis in order to appropriately assess the benefit of ICT.

Introduction

Concurrent chemoradiation (CCRT) is the standard of care for locally advanced head and neck squamous cell carcinoma (LAHNSCC) [1–3]. The addition of induction chemotherapy (ICT) to CCRT has been investigated as a method of further improving outcomes among these patients, but its application remains controversial. Several randomized clinical trials have performed a comparison of ICT followed by CCRT to CCRT alone in LAHNSCC; the majority of these studies have not demonstrated a survival benefit with the addition of ICT [4–8].

Previous studies addressing this question have included a heterogeneous population of all head and neck subsites with both p16-positive and p16-negative disease and varying extent of nodal disease burden. In contrast to the patterns of failure seen in p16-negative disease, distant failure constitutes a considerable portion of treatment failures in p16-positive disease [9,10]. ICT has the potential to improve distant control by eliminating micrometastatic disease; however, this benefit is only likely to be seen in those patients who are at the highest risk for distant failure. At our institution, certain patients with p16-positive oropharyngeal squamous cell carcinoma (OPSCC) with low-neck or N3

Abbreviations: ICT, induction chemotherapy; CCRT, concurrent chemoradiation; OPSCC, oropharyngeal squamous cell carcinoma; HR, hazard ratio

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lymphadenopathy are given ICT prior to CCRT at the discretion of the treating physicians with the objective of lowering the risk of distant failure. In this study, we compared the outcomes of these patients to their counterparts who received upfront CCRT alone.

Material and methods

Study design

A retrospective review was conducted at a single institution from June 2006 to June 2015 after obtaining approval from the institutional review board. Patients eligible for inclusion had stage III-IVB (AJCC 7th Edition staging) histologically-confirmed p16-positive OPSCC with low-neck (level IV and/or Vb involvement) and/or N3 lymphadenopathy. Eighty-eight consecutive patients were identified for inclusion and were definitively managed with either ICT followed by CCRT (n = 44) or CCRT alone (n = 44). Patients who received oncologic surgery of any kind prior to definitive management were excluded from analysis, as were patients with prior head and neck radiotherapy or other known malignancies (excluding non-melanoma skin cancer) within the previous five years. Centralized pathology review was performed on all specimens, with p16 immunohistochemical staining obtained for all cases, with positive cases interpreted to be strong and diffuse, > 70% nuclear and cytoplasmic immunoreactivity [11]. A minimum of one year of follow-up was required for all surviving patients.

Treatment

Among patients who received upfront CCRT, the systemic regimens included triweekly high-dose Cisplatin (n = 19), weekly Cisplatin (n = 5), triweekly high-dose Carboplatin (n = 14), and weekly Cetuximab (n = 6). Patients in the ICT group received Docetaxel and platinum-based chemotherapy with (n = 39) or without (n = 5) 5-Fluorouracil (TPF vs. TP). Following ICT, concurrent regimens consisted of weekly Carboplatin (n = 27), triweekly high-dose Carboplatin (n = 9), weekly Cisplatin (n = 4), triweekly high-dose Cisplatin (n = 3), and weekly Cetuximab (n = 1). Radiation treatment was delivered with intensity-modulated radiation therapy (IMRT) to a planned dose of 70 Gy with simultaneous-integrated boost technique. All patients underwent weekly on-treatment examinations. A treatment break was defined as one lasting two days or longer.

Evaluation with clinical exam and nasopharyngoscopy was performed one month following completion of treatment. Subsequent follow-up was scheduled initially every two to three months and gradually transitioned to every six months until five years at which point patients had the option of annual surveillance in the head and neck clinic or routine care with their primary care provider. The most common follow-up schedule included a three-month post-treatment PET/CT or CT neck and annual chest X-ray. Additional imaging was obtained when clinically indicated i.e., patient reported symptoms or abnormal findings on examination. Post-treatment imaging studies were obtained periodically at the discretion of the treating physician. No planned neck dissections were performed.

Statistical analysis

Patient characteristics and toxicity outcomes were compared with *t*-test for continuous variables and Chi-square test for categorical variables. Outcomes were measured using the length of time from the day of treatment completion to the last day of follow-up. Endpoints analyzed included locoregional recurrence (LRR), distant metastasis (DM), progression-free survival (PFS), and overall survival (OS). Disease control and survival outcomes were estimated by the Kaplan-Meier method. Adjusted hazard ratios (HR) were calculated by a multivariate Cox proportional hazards model accounting for age, T stage, N stage, and smoking status. The statistical significance level was set at 0.05.

Table 1
Patient characteristics.

	CCRT alone	ICT + CCRT	p-value
Median follow-up of surviving patients (months)	36 (13–115)	51 (16–78)	
Median age (years)	61 (35–83)	56 (41–74)	**0.02**
Sex			*> 0.99*
Male	38 (86%)	39 (89%)	
Female	6 (14%)	5 (11%)	
Subsite			0.57
Tonsil	19 (43%)	21 (48%)	
Base of tongue	24 (55%)	23 (52%)	
Soft palate	1 (2%)	0 (0%)	
Current smoker	10 (23%)	8 (18%)	0.79
≥3 drinks per day	9 (20%)	9 (20%)	> 0.99
T stage			0.61
T1	6 (14%)	5 (11%)	
T2	15 (34%)	15 (34%)	
T3	11 (25%)	7 (16%)	
T4	12 (28%)	17 (39%)	
N stage			0.49
N2b	14 (32%)	15 (34%)	
N2c	12 (27%)	16 (36%)	
N3	18 (41%)	13 (30%)	
TNM stage			0.38
IVA	24 (55%)	29 (66%)	
IVB	20 (45%)	15 (34%)	
Low-neck disease	35 (80%)	37 (84%)	0.78
Low-neck and N3 disease	9 (20%)	6 (14%)	0.57

Results

Patient and tumor characteristics

Median follow-up for surviving patients was 47 (range: 13–115) months. Patients who received CCRT alone were older than those who received ICT (61 years vs. 56 years; p = 0.02). Patient groups were otherwise similarly balanced with respect to tumor and nodal stage, presence of low-neck disease, and alcohol and tobacco history. Patient characteristics are listed in Table 1.

Disease control and survival outcomes

Disease control and survival outcomes were estimated by the Kaplan-Meier method, and adjusted HR were calculated to account for confounding factors including age, T stage, N stage, and smoking status. There was no difference observed in LRR rates between patients who received CCRT alone vs. ICT. 3-year LRR: 19% vs. 14% (HR = 0.89 [0.31–2.56]; p = 0.84; adjusted HR = 1.18 [0.38–3.63]; p = 0.78), respectively (Fig. 1). Patients who received CCRT alone experienced a higher rate of distant failure (Fig. 2). 3-year DM: 38% vs. 18% (HR = 0.34–0.15–0.74]; p = 0.009; adjusted HR = 0.32 [0.13–0.82]; p = 0.02). Distant failures were predominantly in isolation, and the most common sites of failure were the lungs followed by the mediastinal and hilar lymph nodes (Table 2). On unadjusted analysis, PFS and OS were inferior in patients who received CCRT alone (Figs. 3 and 4). 3-year PFS: 49% vs. 74% (HR = 0.41 [0.22–0.78]; p = 0.007). 3-year OS: 67% vs. 83% (HR = 0.44 [0.21–0.96]; p = 0.04). After adjusting for confounding variables, ICT was associated with superior PFS (adjusted HR = 0.46 [0.22–0.93]; p = 0.03), but there was no difference in OS (adjusted HR = 0.48 [0.21–1.12]; p = 0.09) between the two groups. Disease control and survival outcomes are outlined in Table 3.