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Definitive chemoradiation for primary oral cavity carcinoma: A single institution experience

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SUMMARY

Objectives: While surgery with or without adjuvant radiation therapy (RT) is the standard of care for oral cavity cancer (OCC), a select group requires nonsurgical treatment. We provide a single-institution experience using definitive chemotherapy and RT for primary OCC.

Materials and methods: We examined 73 patients with previously untreated, non-metastatic primary OCC treated definitively from 1990 to 2011. There were 39 male and 34 female, with a median age of 63 years (range, 35–89). The disease distribution was Stage I and II (7% each), Stage III (14%), and Stage IV (73%). Oral tongue was the most common (48%), followed by floor of mouth (19%), retromolar trigone (13.7%), and others (8.2%). Median tumor dose was 70 Gy. Sixty-two percent of patients ($n = 45$) were treated with concurrent chemotherapy, predominantly platinum-based.

Results: Median follow-up among surviving patients was 73.1 months (interquartile range 14.2–81.4 months). Actuarial 5-year overall survival was 15%. Incidences of locoregional and distant failures were 41.1% and 20.5%, respectively. Kaplan–Meier estimated 5-year rates of locoregional control and freedom from distant metastasis were 37% and 70%, respectively. Mucositis was the most common $\geqslant$Grade 3 acute toxicity (49%). Incidences of Grade 3 late dysphagia and trismus were 15% and 13%, respectively.

Conclusion: This study demonstrates over 20 years of experience using definitive chemoradiation for OCC at our institution. Our results illustrate the challenges in treating patients with advanced disease who are not surgical candidates, and the need for adequate and early treatment to prevent distant disease and improve survival outcomes.

Introduction

Although the worldwide incidence of oral cavity cancer (OCC) has fallen considerably in developed countries in recent years, largely due to the decreased use of tobacco, it remains one of the more common cancers worldwide, with an incidence of 300,000 in 2012 [1–3]. Whereas oropharyngeal cancer (OPC) has been directly linked to the presence of human papillomavirus (HPV), and consequently, there has been a rise in HPV-associated malignancies, the link between OCC and HPV is less clear [1,4]. This is a notable distinction from the established connection to tobacco and alcohol use, which have both been found to be strong risk factors for OPC as well as OCC [4].

National guidelines recommend surgery, often with the addition of postoperative radiotherapy (RT) with or without chemotherapy if adverse pathologic features are present [5]. The 5-year overall survival rates for these tumors have not shown significant improvement with these regimens, remaining between 50% and 60% [5,6]. As continued advancements in reconstructive surgery have led to better cosmetic and functional results, surgical management remains the primary modality of treatment [7].

In patients who are not surgical candidates, either due to medical comorbidity, unresectable disease, or patient preference, definitive RT-based approaches are possible [7,8]. Although treatment employing concurrent chemotherapy and RT (CCRT) has been shown to be advantageous in terms of both local control and overall survival versus RT alone, clinical trials utilizing CCRT for

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advanced OCC patients are limited, largely due to perceptions of unacceptable toxicity and worse efficacy compared to surgery [7,9,10]. A recent single institution retrospective series that evaluated definitive CCRT for patients with advanced (stage III–IV) OCC reported an overall survival rate that exceed 65% with acceptable rates of toxicity [9]. Other studies that have examined primary CCRT also reported promising rates of organ preservation and overall survival, including those patients who presented with tumor invasion of the bone or cartilage [9,11,12].

In our institution, patients who are not candidates for surgery – either with unresectable tumors, locally advanced disease, or concerns about local morbidity – are treated with CCRT. Herein we reviewed our experience in treating locally advanced OCC with primary RT with or without concurrent chemotherapy.

Materials and methods

After obtaining approval from our Institutional Review Board, we retrospectively reviewed the charts of patients at our institution who were diagnosed with previously untreated non-metastatic primary OCC, and subsequently received definitive RT from 1990 to 2011. All oral cavity sites and all stages were included. Charts were reviewed via a computerized database, and data on patient demographics, tumor histology, stage, acute and late toxicity, and radiation and chemotherapy treatments were collected.

Radiotherapy

Patients treated with 2D or 3DCRT were treated with opposed laterals ($n = 50$, 68.5%). Intensity-modulated RT (IMRT) began to be incorporated routinely for patients treated after 2004, and was utilized in all patients by 2006 ($n = 23$, 31.5%). There were eight patients who also received a brachytherapy boost to a median dose of 25 Gy, with a median total tumor dose of 74 Gy (range 70.8–81 Gy). All patients were simulated and treated with the use of an Aquaplast head/neck mask (Aquaplast, Wyckoff, NJ). When cervical lymph nodes (LN) were treated, the shoulders were included in the mask for immobilization. For patients receiving IMRT or 3DCRT, cross-axial images were used to individually outline 3-mm interval slices for delineating target volumes. As patients were not treated surgically, the gross visible tumor on clinical exam and imaging defined the gross tumor volume (GTV). The clinical target volume (CTV) represented areas at high-risk for sub-clinical disease, and was established by evaluation of the primary tumor size along with the extent of involvement of regional LN to establish a margin around the GTV. Typically, there was a 1.0–1.5 cm CTV60-66 margin outlined around primary tumor, and involved nodal regions were included as well. The CTV54 included LN areas that were uninvolved and at lower risk for microscopic spread. At the discretion of the treating radiation oncologist, LN level V was excluded for those with node-negative disease; levels Ib, II, III, IV were always included in the radiation portal.

Margins of 0.3 cm were added to define the planning target volume (PTV): the gross tumor constituted the PTV70, high-risk subclinical disease established the PTV60-66, while low-risk subclinical disease was included in the PTV54. For those who received 3DCRT or IMRT, normal structures were outlined, including the brainstem, spinal cord, optic nerves and chiasm, right and left cochlea, parotid glands, and mandible.

Chemotherapy

Patients treated since 2000 were given concurrent systemic chemotherapy. The majority of patients who were treated with chemotherapy received single-agent cisplatin ($n = 23$, 31.5%) during RT, with planned two to three cycles (100 mg/m^2) on days 1, 22, and 43; an additional 4% of patients received cisplatin with a second agent. As an alternative, based on potential toxicities, pre-existing medical conditions, and patient preference, carboplatin was given alone (70 mg/m^2), or in combination with either 5-fluorouracil (600 mg/m^2) or paclitaxel (50 mg/m^2), to 19% of patients, for 4 days as a daily continuous infusion. Other patients were given single-agent cetuximab, or in combination with paclitaxel, with an initial loading dose (400 mg/m^2), followed by seven weekly cycles (250 mg/m^2).

Follow-up

Patients were evaluated on a weekly basis by the treating radiation oncologist while undergoing RT. Post-treatment, patients were evaluated every 2–3 months for 2 years, and every 4–6 months thereafter in coordination with the radiation oncologist, medical oncologist, and surgical oncologist. Each follow-up visit consisted of a comprehensive head and neck examination and a flexible fiberoptic endoscopy when indicated. Toxicities at each visit were graded utilizing the Common Toxicity Criteria for Adverse Events (CTCAE) v4.0. Approximately 3 months after

Table 1
Patient and treatment characteristics.

	N	%
Gender		
Male	39	(53.4)
Female	34	(46.6)
Smoking		
>10 pack years	47	(64.4)
<10 pack years	19	(26.0)
Unknown	7	(9.6)
Disease site		
Oral tongue	35	(47.9)
Floor of mouth	14	(19.2)
Retromolar trigone	10	(13.7)
Buccal mucosa	4	(5.5)
Gingiva	4	(5.5)
Lip	2	(2.7)
Hard palate	2	(2.7)
Alveolar ridge	2	(2.7)
T stage		
T1	5	(6.8)
T2	10	(13.7)
T3	11	(15.1)
T4	47	(64.4)
N stage		
N0	24	(32.9)
N1	12	(16.4)
N2	31	(42.5)
N3	6	(8.2)
AJCC stage		
I	5	(6.8)
II	5	(6.8)
III	10	(13.7)
IV	53	(72.6)
Histology		
SCC	73	(100)
Chemotherapy		
Concurrent	45	(61.6)
Cisplatin	23	(31.5)
Carboplatin/5-FU	6	(8.2)
Carboplatin/paclitaxel	6	(8.2)
Cetuximab	4	(5.5)
Other	10	(13.7)
None	24	(32.9)

Abbreviations: SCC = squamous cell carcinoma; 5-FU = 5-fluorouracil.