Outcomes of oral cavity cancer patients treated with surgery followed by postoperative intensity modulated radiation therapy.

Sean Quinlan-Davidson MD
Lehigh Valley Health Network, sean.quinlan@lvhn.org

Abdallah S R Mohamed

Jeffrey N Myers

Gary B Gunn

Faye M Johnson

See next page for additional authors

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Outcomes of oral cavity cancer patients treated with surgery followed by postoperative intensity modulated radiation therapy

Sean R. Quinlan-Davidson [a,d], Abdallah S.R. Mohamed [a,e], Jeffrey N. Myers [b], Gary B. Gunn [a], Faye M. Johnson [c,f], Heath Skinner [a], Beth M. Beadle [a], Ann M. Gillenwater [a], Jack Phan [a], Steven J. Frank [a], William N. William [c], Andrew J. Wong [a], Stephen Y. Lai [b], Clifton D. Fuller [a], William H. Morrison [a], David I. Rosenthal [a], Adam S. Garden [a,*]

[a] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[c] Department of Thoracic/Head and Neck Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Department of Radiation Oncology, Allentown Radiation Oncology Associates, Allentown, PA, USA
[e] Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, University of Alexandria, Alexandria, Egypt
[f] The University of Texas Graduate School of Biomedical Sciences, Houston, TX, USA

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ABSTRACT

Objectives: Although treatment paradigms have not changed significantly, radiotherapy, surgery, and imaging techniques have improved, leading us to investigate oncologic and survival outcomes for oral cavity squamous cell cancer (OCSCC) patients treated with surgery followed by postoperative IMRT.
Material and methods: Records of patients with pathological diagnosis of OCSCC treated between 2000 and 2012 were retrospectively reviewed. Patients' demographic, disease, and treatment criteria were extracted. Kaplan-Meier method was used to calculate survival curves.
Results: Two hundred eighty-nine patients were analyzed. Median follow-up was 35 months. Two hundred sixty-eight had neck dissections (93%), of which 66% had nodal involvement, and 51% of those positive dissections had extracapsular extension. Forty patients received induction chemotherapy and 107 received concurrent chemotherapy. Median dose to high risk clinical target volume was 60 Gy/30 fractions. The 5-year locoregional control and overall survival rates were 76% and 57%, respectively. Tumors with >1.5 cm depth of invasion had significantly higher risk of local failure compared with $\leq$1.5 cm ($p < 0.001$). In multivariate analysis, positive and no neck dissection ($p = 0.01$), positive lymphovascular invasion ($p = 0.006$) and >1.5 cm depth of invasion ($p = 0.003$) were independent predictors of poorer survival.
Conclusions: Disease outcomes were consistent with historical data and did not appear compromised by the use of IMRT.

Introduction

Locally advanced oral cavity squamous cell carcinoma (OCSCC) is standardly treated with surgery. Adjuvant postoperative radiation therapy is recommended for patients with adverse features including: stage IV disease, inadequate margins, and invasion of tumor into perineural spaces, lymphovascular spaces or bone. Over the last decade, the addition of chemotherapy to adjuvant radiation was recommended, particularly for patients who have 'high risk' pathologic features which include extracapsular nodal extension (ECE) and/or a positive surgical margin.

Except for the recent inclusion of chemotherapy for selected patients, this management strategy has remained unchanged over nearly half a century. However, while the overall strategy has not changed, there have been improvements in specific components of management. Clinical staging has improved with the continual improvement in imaging. Surgical approaches have changed as well. The addition of elective neck dissection for node negative patients improves their survival [1]. Further, surgical techniques continue to improve, particularly the ability to repair large oral defects with soft tissue and osteocutaneous grafts. Radiation tech-

* Corresponding author at: Head and Neck Section, Department of Radiation Oncology, Unit 97, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA.
E-mail address: agarden@mdanderson.org (A.S. Garden).

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niques have also evolved. Intensity modulated radiotherapy (IMRT) is an advanced radiation treatment planning and delivery technique that was introduced early this century. This technique has largely replaced conventional head and neck radiotherapy techniques as it allows improved target conformality while sparing some normal tissues. Studies have supported the benefit of IMRT for treatment of patients with head and neck carcinoma treatments, delivering high dose to targets while minimizing dose to normal structures [2,3]. However, most head and neck studies of IMRT have focused on the treatment of patients with oro- and naso-pharyngeal cancers, and patients treated without surgery.

The aims of this retrospective study was to assess the oncologic and survival outcomes of patients with locally advanced OCSCC treated with modern approaches with a focus on the use of postoperative IMRT.

Methods

Patients

The database maintained by the Department of Radiation Oncology at The University of Texas M.D. Anderson Cancer Center (MDACC) was searched to identify patients treated with postoperative IMRT for OCSCC between 2000 and 2012. Our institutional review board granted permission to conduct this retrospective study.

Patients with distant metastases or concurrent malignancies at the time of diagnosis, a previously treated malignancy of the head and neck or previous radiation to the head or neck, a history of any malignancy (excluding non-melanomatous skin cancer) within two years of diagnosis, tumors with non-squamous cell carcinoma histology, or treatment with chemotherapy prior to staging at MDACC were excluded.

Medical records were reviewed to assess patients' demographic, clinical, radiologic and pathologic data. Patients' disease was staged according to the AJCC 2010 staging system [4]. Charts were reviewed to verify tumor size and sites of invasion.

Treatment

The overall treatment strategies were individualized for each patient. General treatment strategies were recommended at our multidisciplinary tumor board, though specifics of treatment were carried out by the individual patients' treatment teams. Our general approach during the years of this study was that OCSCC are managed with surgery, with radiation and chemotherapy used adjuvantly. Induction chemotherapy was recommended for selected patients. Radiation was used post-operatively, and patients were assessed for concurrent chemoradiation based on pathologic findings, and comorbidities.

All patients were irradiated with IMRT. Three clinical target volumes (CTVs) were typically defined. CTV1 was defined as the preoperative tumor bed with margin (1–2 cm). CTV2 was defined as the operative bed exclusive of CTV1, and CTV3 was defined as subclinical sites at risk not operated. Doses prescribed to these 3 targets were 60, 57, and 54 Gy, respectively; treatment was delivered in 30 fractions. Occasionally a high-risk volume was identified that received higher dose (63–66 Gy) typically in cases of extracapsular nodal extension (ECE), positive margin or questionable margin status. Dosing was individualized for patients that were found to have recurrent disease at the start of their radiation.

The initial IMRT planning system, Corvus system (North American Scientific, Inc., Cranberry Township, PA) was used from 2000 to 2003; in 2003 we transitioned to the Pinnacle planning system (Philips Medical Systems, Andover, MA). Treatment was delivered with a static gantry approach. The template for patients treated to both sides of the neck used 9 beams set equidistant through 360°. Patients treated to only 1 side of the neck were planned with a template using 7 beams equidistant through a 190° arc. Beam angles and number were modified during the optimization process. IMRT was delivered using Varian (Varian Medical Systems, Palo Alto, CA) linear accelerators delivering 6-MV photons.

In general, IMRT was used to treat the primary tumor and upper neck nodes. For patients treated with split field technique, the isocenter was set above the arytenoids, and IMRT was delivered to portals above the isocenter, whereas the lower neck below the isocenter was treated with an anterior beam, with a larynx and/or full midline block. If there was nodal disease identified in levels 3 to 4 clinically or at surgery, these levels were boosted with glancing photon beams and/or electron beams. A "whole-field" IMRT approach was used in situations in which the patients' anatomy or primary tumor location created concerns that tumor might be underdosed using the "split-field" approach. Common scenarios in which a whole field approach was used were in patients who had reconstruction where the flap thickness made splitting undesirable.

Follow-up

Weekly evaluations were done by the treating radiation oncologist for all patients during radiation treatment. The first posttreatment follow-up was at 8–12 weeks after radiation completion and subsequently every 2–3 months for the first year, every 3–4 months for the second year, and at least twice a year for up to 5 years.

Statistical analysis

Chi-squared tests were used to compare proportions between subsets. Binary logistic regression was used to test the relationship between continuous variables and binary responses. The Kaplan-Meier method was used to calculate actuarial curves. The last day of radiation therapy was used as time zero. Comparisons between survival curves were made using the log-rank test. Stepwise multivariate analysis was performed using the Cox proportional model via backward selection with variable inclusion when $p < 0.10$. For continuous variables with significant association with outcome endpoints, recursive partitioning analysis (RPA) was done to identify optimal cutoff points. All analyses were performed using JMP Pro statistical software version 11.2.0 (SAS Institute Inc, Cary, NC). P values less than 0.05 were considered significant.

Results

Patients

We identified 289 patients who met the inclusion criteria. Table 1 details patient demographics, staging, and disease characteristics. Of the entire cohort, 24 patients (8%) used chewing tobacco or betel Quid. One hundred sixteen were never cigarette smokers (40%), though 19 used other tobacco products. Among those who had smoked cigarettes, the median pack-year was 30 (range 1–150).

Surgery

All patients received surgery to the primary tumor. One hundred eighty-seven patients (65%) had a free flap inserted during surgical reconstruction. Pathologic T-category is shown in Supplementary Table S1. Eight patients had a positive margin and 44

Table 1
Patient and disease characteristics.

Characteristics	No. (%)
Sex	
Male	189 (65)
Female	100 (35)
Age, median	58.9 years (range, 20–88 years)
Primary site	
Tongue	147 (51)
Gingiva	48 (16)
Retromolar trigone	32 (11)
Buccal	28 (10)
Floor of mouth	26 (9)
Hard palate	8 (3)
Smoking	
Current	104 (36)
Former	69 (24)
Never	116 (40)
Alcohol	
None	110 (38)
<1 drink per week	54 (19)
≥1 drink per week	110 (38)
Heavy (but quit)	15 (5)
Premalignant lesion	
Yes	73 (25)
No	216 (75)
cT-category	
1	27 (9)
2	124 (43)
3	39 (14)
4a	83 (29)
4b	7 (2)
x	9 (3)
cN-category	
0	108 (37)
1	50 (17)
2a	2 (1)
2b	99 (35)
2c	26 (9)
x	4 (1)
Tumor differentiation	
Well	39 (13)
Moderate	164 (57)
Poor	84 (29)
Unspecified	2 (1)
Margin status	
Positive	8 (3)
Close (<5 mm)	44 (15)
Negative	237 (82)
Depth of invasion	
≤1.5 cm	191 (66)
>1.5 cm	71 (25)
Unspecified	27 (9)
Perineural invasion	
Yes	132 (46)
No	153 (53)
Unspecified	4 (1)
Lymphovascular invasion	
Yes	56 (19)
No	159 (55)
Unspecified	74 (26)
Extracapsular extension	
Yes	91 (31)
No	198 (69)

patients had a close margin (<5 mm). Eighty-four tumors (29%) were poorly differentiated, 132 (46%) had perineural invasion, and 56 (19%) had lymphovascular invasion. Depth of invasion (DOI) was measured in 263 tumors, and the median DOI was 1.1 cm.

Two-hundred sixty eight patients (93%) had a neck dissection, 64 of which were bilateral neck dissections. Neck dissections were described as selective (206 patients), modified radical (60 patients) and radical (2 patients). The median number of lymph nodes examined was 32. Thirty-eight patients (14%) had <20 nodes examined from their neck dissection specimens.

Among the 108 patients who presented with clinically negative nodes, 83% had elective neck dissection. The rate of pathologically positive neck disease in those patients was 51%. Of the 181 patients with clinically positive nodes 178 (98%) had neck dissection. The rate of pathologically positive neck disease in those patients was 70%.

Pathologic N-category is shown in Supplementary Table S1. One-hundred seventy patients (63%) had positive neck dissections, of which a median number of 1 lymph node was positive (range, 1–18 positive lymph nodes). Ninety-one patients (31% of all patients and 53% of patients with pathologic positive nodes) had nodes with extracapsular extension (ECE).

Twenty-one patients did not have a neck dissection. Fifteen had cancers involving the superior aspect of the oral cavity, and had infrastructure maxillectomies. Six had oral tongue cancer. Of these 6, four presented with glossectomies done without neck dissection outside of MDACC. All 6 were clinically node negative and clinical – surgical – pathologic findings dictated a need for adjuvant radiation for the primary tumor, so neck dissections were not performed.

Chemotherapy

Forty-one patients received induction chemotherapy. Nine of these patients were treated on study with preoperative erlotinib. The remaining 32 patients were treated with taxane-platin based induction chemotherapy. A third drug was used in 22 of these patients; 5-flourouracil, 10 patients, cetuximab, 9 patients, and ifosfamide, 3 patients. Of the 41 patients who received induction chemotherapy, 21 patients (51%) had T4 disease and 32 patients (78%) had N2b or N2c disease at presentation.

One hundred seven patients received concurrent chemotherapy. Of those, sixty-nine patients (64%) had ECE and 22 patients (21%) had close or positive margins. Thirty-nine patients received high dose cisplatin (75–100 mg/m^2) and 39 patients received weekly cisplatin (20–40 mg/m^2). Sixteen patients received weekly carboplatin as single agent (13) or combined with paclitaxel (3). Twelve patients received cetuximab, as either a single agent (5), or as a doublet combined with cisplatin (4), or docetaxel (3). One patient received vandetinib. Twenty of these 107 patients also had induction chemotherapy.

Radiotherapy

Two-hundred forty-two patients' radiation was delivered using a split-field technique (83%). Forty-six patients, 21 whom were node positive, received ipsilateral radiotherapy (16 gingiva; 11 RMT; 9 buccal; 6 oral tongue; 4 hard palate). The median dose to the CTV1 was 60 Gy (range, 13–74 Gy). The median fraction number was 30. Two patients did not receive neck radiotherapy; both had pT2 N0 tongue cancers. Twelve patients had an unplanned break in radiotherapy (range 1–10 days) and 8 patients did not complete their course of radiotherapy either due to choice (4) or prohibitive medical events (4).

Fourteen patients (5%) were found to have gross disease either just prior to their planned radiation, or during their course of radiation. Ten had disease in the operative bed and 4 patients had gross disease in an unoperated neck. Their radiation therapy schedules were modified to address these findings. Eleven of these patients' gross disease was treated to doses ranging from 66 to 74 Gy. One

patient died at 53 Gy, and 2 patients who had disease in an undissected neck had disease treated to 60 Gy with preoperative intent, while the operative beds were treated with postoperative intent. Eleven of these patients with gross disease at radiation were also treated with concurrent chemotherapy. Of the 3 patients who did not have chemotherapy, one was planned for surgery, one was elderly with poor PS and one refused.

Outcomes

The median follow-up time was 35 months (range 1–179). Sixty-three patients (22%) developed locoregional recurrences; 31 developed recurrence at the primary tumor site, 20 in the neck, and 12 in both the primary site and neck. The median time to recurrence was 4 months (range 0–71). Fifty-two recurrences (83%) occurred within one year post-treatment.

Local control

The actuarial 2- and 5- year local control rates were 86% and 83%, respectively. In multivariate analysis, the depth of primary tumor invasion was a strong independent predictor of local control, as tumors with >1.5 cm (RPA driven cutoff) depth of invasion (n = 71, T1 (1); T2 (17); T3 (20); T4 (32)) had significantly higher risk of local failure compared with ≤1.5 cm (HR, 5.4; 95% CI 2.1–14.1, $p < 0.001$). Local recurrence was also greater in patients with positive margins ($p < 0.001$). Primary tumor subsite was associated with local failure in univariate analysis ($p = 0.004$), as local control was better in patients with oral tongue/floor of mouth primaries compared to other oral primaries, but in multivariate analysis it was not statistically significant ($p = 0.4$). There was also improved local control ($p = 0.01$) in multivariate analysis for patients who were reconstructed with free flaps. Smoking pack-year history was another independent factor associated with local control, as patients with ≥20 pack-year had better local control compared with <20 ($p = 0.04$). There was a sequential worsening of local control with increasing T-category (pathologic), though the overall analysis was not significant ($p = 0.3$). Additional analysis of the effect of tumor depth of invasion in different subsites, showed it was more profound in tongue/floor of mouth primaries compared with other subsites ($p = 0.01$). Fig 1 shows the local control by depth of invasion in tongue/floor of mouth primaries compared with other subsites.

Regional control

The actuarial 2- and 5- year regional control rates were 88% and 87%, respectively. The preoperative clinical nodal status was not associated with regional control. The 5-year regional control rate for patients who presented with clinically negative nodes was not statistically different compared with patients who presented with clinically positive nodes (86% vs. 88%, respectively; $p = 0.8$, Fig 2A). However, the neck dissection status was an independent predictor of regional control among all tested variables ($p = 0.036$). The 5-year regional control rate was superior for patients with negative neck dissection (n = 98) compared with positive neck dissection and no dissection (94% vs. 85% and 70%, respectively; $p < 0.001$, Fig 2B). Lower level nodal involvement (levels III, IV, and V) was also associated with worse regional control compared with levels I and II (HR 6.7, 95% CI1.9–32.9, $p = 0.002$). There was no difference in regional control between those with and without nodal extracapsular extension.

Locoregional control

The actuarial 2- and 5- year locoregional control rates were 79% and 76%, respectively (Fig 3A). Among the 14 patients who had already developed locoregional recurrence 8 had persistent disease at the end of therapy and are included among the 63 patients described above. There were no differences in locoregional control in patients who received chemotherapy (neoadjuvant and concurrent modes tested separately). However, when analyzing the use of concurrent chemotherapy for only those patients with high-risk features (inadequate margins, extracapsular nodal spread), patients treated with concurrent chemotherapy did have improved locoregional control ($p = 0.016$, Supplementary Fig. S1). In multivariate analysis of correlates of combined locoregional failure; tumor depth of invasion, positive margins, free flap reconstruction, neck dissection status, and smoking pack-year history remained statistically significant ($p < 0.05$ for all).

As some of the variables tested were based on pathologic findings, and induction therapy can influence these findings, the multivariate analysis was redone excluding patients who had received induction chemotherapy. The 5 variables described above remained the only statistically significant variables.

Distant control

Forty-two patients developed distant metastases, 27 of whom also had locoregional control. The actuarial 2- and 5- year distant

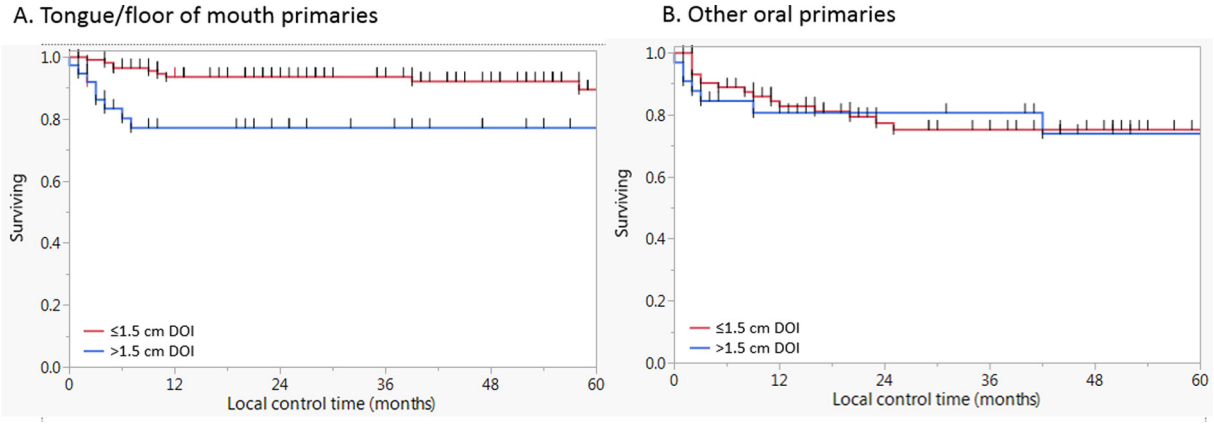

Fig. 1. Kaplan-Meier curves calculated for patients with (A) tongue/floor of mouth primaries, where patients with >1.5 cm depth of invasion (DOI) had significantly worse 5-year local control (90% vs. 77%, $p = 0.007$), while for other oral primaries (B) there was no significant difference. Short vertical lines represent censored data.

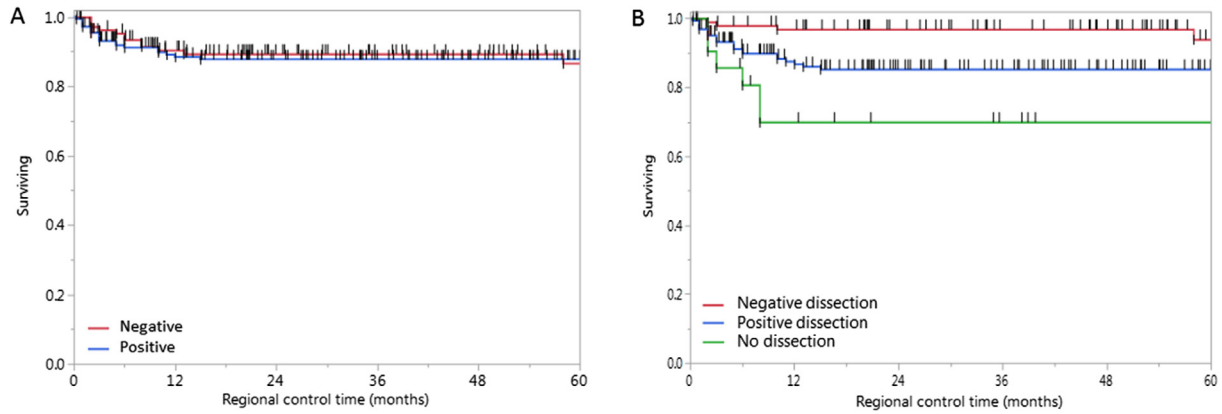

Fig. 2. Kaplan-Meier curves calculated for all patients (n = 289) showing regional control by clinical nodal status at presentation (A), and by surgical dissection status (B). Short vertical lines represent censored data.

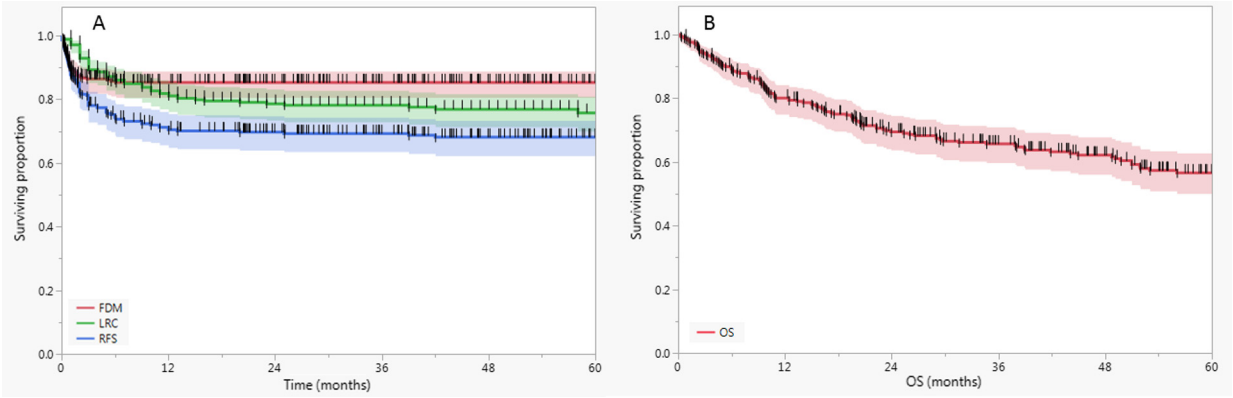

Fig. 3. Kaplan-Meier curves calculated for all patients (n = 289) showing in panel (A) locoregional control (LRC), freedom from distant metastasis (FDM), and relapse free survival (RFS); and in panel (B) the overall survival (OS). Shaded colors represent 95% confidence intervals, short vertical lines represent censored data.

control rates were both 85% (Fig 3A). Distant sites included: lung, 31 patients; dermal, 8; bone, 6; liver, 2; and brain, 1. Thirty-six (92%) of these patients were node positive. Limiting analysis to patients with locoregional control, multivariate analysis showed lymphovascular space invasion as the strongest independent predictor of distant failure (HR 10.6, 95% CI 3.2–45.0, $p < 0.001$). History of oral premalignancy ($p = 0.02$), nodal dissection status ($p = 0.02$), and smoking pack-year history ($p = 0.04$) were among the significant correlates of distant failure. There were no differences in distant metastases in patients who did or did not get induction chemotherapy or concurrent chemotherapy. The multivariate analysis was redone excluding patients who had received induction chemotherapy. A history of oral premalignancy was not significant in this reanalysis ($p = 0.2$).

Overall survival

One hundred eighteen patients (41%) have died. Only 8 of the 63 patients (13%) who had locoregional recurrences are alive, 34–83 months from the end of radiation. All patients with distant recurrences died. The 2- and 5- year overall survival rates were 69% and 57%, respectively (Fig 3B). Among the 36 patients who died without recurrence on last follow-up, the causes of death were: unknown, 18 patients; second primary cancer, 9 patients; non-cancer death, 6 patients; and possibly related to treatment effects, 3 patients.

Univariate and multivariate analysis of overall survival correlates is presented in Table 2. It shows that in multivariate analysis, neck dissection status ($p = 0.01$), lymphovascular invasion ($p = 0.006$) and depth of invasion ($p = 0.003$) were independent predictors of overall survival. The 5-year overall survival rate was better for patients with negative vs. positive or no neck dissection (77% vs. 57%, $p < 0.0001$, Fig 4A); negative vs. positive lymphovascular invasion (61% vs. 43%, $p = 0.0006$, Fig 4B); and $\leq$1.5 cm vs. >1.5 cm depth of invasion (60% vs. 40%, $p = 0.002$, Fig 4C). The multivariate analysis was redone excluding patients who had received induction chemotherapy. The 3 variables above remained the only statistically significant variables.

Second primary tumors

Twelve patients developed second primary tumors (SPTs) subsequent to their radiation. Sites of SPTs included: Head and neck, 4; lung, 4; gastrointestinal, 3; and genitourinary, 1. Within the head and neck, the subsites involved were: oral tongue, 2; true vocal cord, 1; and posterior pharyngeal wall, 1. The cancers in the oral tongue were on the contralateral aspect of the tongue, and were thus deemed SPTs. Among the 4 patients that developed lung cancer, 2 were squamous, and while the clinical presentation favored a primary lung tumor, these 2 patients were also coded as having distant disease.

Osteoradionecrosis

Twenty patients (7%) developed osteoradionecrosis (ORN). Fifteen required surgery and 5 were treated with hyperbaric oxygen

Table 2
Univariate and multi variate Cox regression analysis of overall survival.

Characteristics		Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Age	Continuous variable	–	0.01*	–	0.5
Sex	Male	1		–	
	Female	0.99 (0.7–1.5)	0.3	–	–
Site	Oral tongue/FOM	1		1	
	Other subsites	1.4 (0.96–1.98)	0.08	1.2 (0.7–1.9)	0.5
cT stage	cT1-cT2	1		–	
	cT3-cT4	1.3 (0.9–1.9)	0.14	–	–
pT stage	pT1-pT2	1		–	
	pT3-pT4	1.3 (0.9–1.9)	0.15	–	–
cN stage	cN0	1			
	cN1-cN3	1.1 (0.8–1.6)	0.57	–	–
Neck dissection status	Negative (pN0)	1		1	
	Others (pN + & no dissection)	2.94 (1.9–4.8)	0.0001*	2.2 (1.1–3.9)	0.01*
Nodal level	Levels I and II	1		–	
	Levels III, IV, and V	1.4 (0.9–2.2)	0.14	–	–
Smoking status	Never	1		–	–
	Former	0.92 (0.6–1.5)	0.7	–	–
	Current	0.93 (0.6–1.4)	0.7	–	–
Smoking pack-year	≥20 pack-year	1		–	
	<20 pack-year	1.3 (0.9–1.8)	0.2	–	–
Alcohol history	No	1		–	
	Yes	1.2 (0.8–1.8)	0.4	–	–
History of oral premalignancy	No	1		–	
	Yes	1.2 (0.3–1.8)	0.3	–	–
Depth of invasion	≤1.5 cm	1		1	
	>1.5 cm	1.5 (1.04–2.2)	0.03*	2.1 (1.3–3.5)	0.003*
Extracapsular extension	No	1		1	
	Yes	1.8 (1.2–2.6)	0.003*	1.6 (0.8–3.2)	0.2
Lymphovascular invasion	No	1		1	
	Yes	2.1 (1.4–3.2)	0.001*	1.95 (1.2–3.1)	0.006*
Perineural invasion	No	1		–	–
	Yes	1.05 (0.7–1.5)	0.8	–	–
Margin status	Positive	1		1	
	Others	0.4 (0.2–1.1)	0.08	3.2 (0.5–11.7)	0.18
Free flap reconstruction	No	1		–	–
	Yes	1.2 (0.8–1.8)	0.4	–	–
Radiation dose	Continuous variable	–	0.9	–	–
Concurrent chemotherapy	No	1		–	
	Yes	1.2 (0.8–1.7)	0.4	–	–
Induction chemotherapy	No	1		–	
	Yes	1.1 (0.6–1.8)	0.7	–	–

therapy. Development of ORN was associated with smoking (>20 pack year, p = 0.003), males (p = 0.056), and bone invasion of tumor (p = 0.09).

Discussion

Developed and tested in the early part of this century, IMRT has largely become the standard mode of treatment planning and delivery for head and neck cancer. Subsequent to the seminal RTOG 95–01 postoperative trial testing chemoradiation [5], the RTOG has initiated 3 postoperative trials. RTOG 234 [6] was amended in 2005 to allow for IMRT, and the 2 current active studies, RTOG 920 and 1216, with planned accrual of over 1400 patients, are IMRT based studies. However, in comparison to oropharyngeal and nasopharyngeal cancers, for which IMRT has been tested in cooperative trials (both phase II and III) [3,7], and in large retrospective [8] and multi-institutional settings [9], the data regarding outcomes using IMRT in the postoperative setting, and specifically for the treatment of oral cancer is more limited.

Our current study adds nearly 300 patients' outcomes to this literature. Not surprising, as IMRT is principally used to spare normal tissues and not to enhance disease control, our 5-year locoregional control rate of 76% and overall survival rate of 57% is consistent with both older postoperative experiences using conventional approaches [10,11] and more recent smaller retrospective series testing IMRT [12,13]. More importantly, the use of IMRT did not demonstrate a compromise in disease control.

Our patient demographics included a large group of never-smokers who had poorer disease control than smokers. However, recent analysis of the genetics of oral cancers has not demonstrated major biologic differences between tumors of smokers and non-smokers [14]. Buccal, maxillary gingiva, and hard palate tumors represent a small percentage of oral cavity cancers yet represented 30% of our cohort. Previous studies are largely limited to retrospective cohorts, with the recurring conclusion that squamous cell carcinomas tumors of these sub-sites of the oral cavity are aggressive in nature [15]. We similarly found that patients with primaries of these sites had a poorer local control (p = 0.004).

Our results demonstrate a significant association between the depth of primary tumor invasion and local control particularly in oral tongue and floor of mouth primaries. This effect was noted in tumors with >1.5 cm depth of invasion and was reflected on worse overall survival for those patients. The depth of invasion is a well-established predictor of occult nodal metastasis in the literature for early T1-T2 oral disease with clinically negative neck [16]. However, the impact of depth of invasion on local control in patients treated with surgical resection followed by IMRT is less established and our results suggest that oral tongue and floor of mouth primaries with deeper tumor invasion may be candidates for dose escalation given the relatively higher local relapse rate.

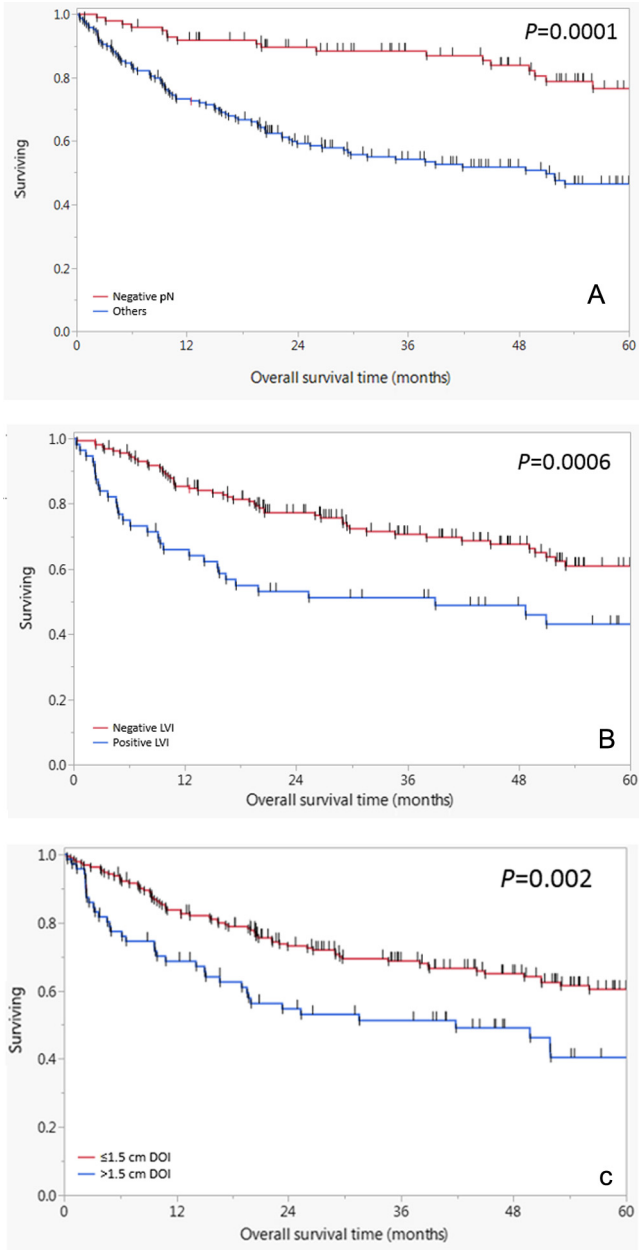

Fig. 4. Kaplan-Meier curves showing a significantly superior overall survival for patients (A) with neck dissection status, (B) with negative lymphovascular invasion (LVI), and (C) with depth of invasion (DOI) $\leq$ 1.5 cm. Short vertical lines represent censored data.

Local recurrence was also greater in patients with positive margins, though only 8 patients had positive margins, and there was no significant difference in local control for close margins compared to negative margins. Free flap reconstruction was also an independent predictor for better local and locoregional control but this was not reflected into better overall survival possibly due to the diversity of oral cavity subsites and stages of disease in the studied cohort [17].

Matching the results of several other reports, negative neck dissection was a strong predictor of regional control and overall survival. However, contrary to many other reports, lymphovascular invasion was an independent predictor of distant control and overall survival. This finding aligns with a report from Jones et al. [18] who also describe the independent prognostic impact of lymphovascular invasion.

We report a 7% incidence of ORN. This is consistent with other recent reports exploring IMRT for oral cavity cancers, or reports on the incidence of ORN in patients treated with IMRT for head and neck cancers [19,20]. Studer et al. recently reported a 17% incidence of ORN in patients with oral cavity cancers treated with postoperative IMRT who received >60 Gy to the mandible [19]. A recent SEER medicare analysis of jaw complications in patients treated for oral cancers showed that patients treated with non-IMRT had 17% event rate compared to 14% in patients treated with IMRT [21]. A more robust analysis of dose-volume correlates was beyond the scope of this paper, though we did observe a trend for an increased incidence of ORN if tumor invaded bone. It is important to note that most patients, if not all, had high dose planning targets that extended into bone due to tumor location, and while our planning goals tried to minimize dose beyond our prescription dose to targets, mandible (or maxilla) avoidance goals were otherwise not used.

Our results are, however, limited by its retrospective nature and the inclusion of different primary tumor subsites within the oral cavity as well as wide variety of disease stage. Additionally, the selection of chemotherapy agents, timing, and combination with radiotherapy was diverse. Nevertheless, our report represents a largescale series of nearly 300 patients with oral cavity cancer treated with surgery followed by postoperative IMRT and shows that disease outcomes were favorable, and not compromised by the use of IMRT.

The use of concurrent chemotherapy was associated with better locoregional control in patients with accepted high risk features (ECE in particular). However, while outcomes did not appear compromised with IMRT and the selective use of chemotherapy, with just over half the patients surviving 5-years, treatment approaches clearly need improvement. As a secondary goal of this work, we have identified several variables suggesting poorer outcomes, some well accepted, while others, such as depth of invasion > 1.5 cm, less well studied. In the absence of clear molecular biomarkers or viral association to dictate groups with OCSCC with clear differing prognoses, these variables may be hypothesis-generating for treatment intensification or novel approaches.

In conclusion, our results show 5-year locoregional control and overall survival rates of 76% and 57%, respectively, consistent with outcomes expected for this population. Thus IMRT, a radiation strategy based on delivering the desired dose to targets deemed at risk for harboring microscopic disease while avoiding normal tissues did not compromise expected disease control.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2017.07.002.

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