Published in final edited form as:

Laryngoscope. 2018 November ; 128(11): 2539–2545. doi:10.1002/lary.27191.

Long-term outcomes in oral cavity squamous cell carcinoma with adjuvant and salvage radiotherapy after surgery

Evangelia Katsoulakis, M.D.^{*}, Jonathan E. Leeman, M.D.^{*}, Benjamin H. Lok, M.D.^{*}, Weiwei Shi, M.S.[‡], Zhigang Zhang, PhD[‡], Jillian C. Tsai, M.D.^{*}, Sean M. McBride, M.D.^{*}, Eric J. Sherman, M.D.[#], Marc Cohen, M.D.[†], Richard Wong, M.D.[†], Ian Ganly, M.D., Ph.D.[†], Nancy Y. Lee, M.D.^{*}, and Nadeem Riaz, M.D.^{*}

^{*}Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

[†]Department of Surgical Oncology ENT, Memorial Sloan-Kettering Cancer Center, New York, NY

[‡]Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

[#]Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Objective—Early stage oral cavity squamous cell carcinoma (OCSCC) represents a heterogeneous group of patients and loco-regional recurrence rates are as high as 25% with surgery alone. Radiotherapy is typically reserved as part of salvage multimodality therapy after salvage surgery, as it is generally thought that there is no significant detriment to salvage therapy. Our aim was to examine outcomes for recurrent OCSCC treated with salvage surgery and radiation and compare them to outcomes for patients treated with adjuvant post-operative RT upfront.

Methods—We identified 425 patients with OCSCC treated with post-operative RT at our institution. The 5-year rates of local failure, locoregional failure, survival and distant metastasis were the main outcome measures. We performed a landmark analysis and examined the same outcomes in the adjuvant versus salvage cohorts using Cox proportional hazards and Fine-Gray competing risk method.

Results—The adjuvant cohort had higher tumor (T) ($p < 0.0001$) and nodal (N) ($p < 0.0001$) stage than the salvage cohort's stage at initial presentation. On multivariate analysis, a strategy of salvage RT experienced poorer OS compared to upfront adjuvant RT (HR 1.84, 95% CI 1.26–2.70, $p = 0.002$). Moreover, salvage surgery followed by RT patients experienced increasing risk of LRF (HR 1.56, 95% CI 1.18–2.06, $p = 0.002$) and distant metastasis (HR 1.53, 95% CI 1.08–2.17, $p = 0.02$) on multivariate analysis. Additional analysis was performed excluding salvage cohort with advanced disease at initial presentation (T3–T4 and N2). Salvage RT treatment selection for early stage OCSCC continued to experience significantly poorer OS as compared to adjuvant RT (HR 1.48, 95% CI 1.002–2.19, $p = 0.049$).

Reprint requests: Nadeem Riaz, M.D., 1275 York Avenue, New York, NY, 10065, Tel: (646) 888-3495, riazn@mskcc.org.

Conflicts of Interest: No potential conflicts of interest exist.

Meeting: Presented at the 59th annual meeting-American Society for Radiation Oncology (ASTRO) 9/24/17.

Level of evidence: 4

Conclusion—Early stage OCSCC patients who are observed and experience recurrence requiring salvage therapy (surgery and radiotherapy) have worse oncologic outcomes than locally advanced patients receiving upfront adjuvant radiotherapy. Prospective randomized studies are needed to identify high-risk subset of early stage OCSCC comparing adjuvant RT versus observation followed by salvage surgery and RT at recurrence.

Keywords

adjuvant radiation; salvage radiation; oral cavity squamous cell carcinoma

INTRODUCTION

Oral cavity squamous cell carcinoma is a common cancer with approximately 30,260 new cases and 6,650 deaths annually in the US¹. Worldwide, an estimated 405,000 new cases of OCSCC are diagnosed ever year². Notwithstanding a global trend for decreased smoking and alcohol use, the incidence of OCSCC has remained stable in the US and sharply risen in Europe³. Cancers of the oral cavity are typically treated with surgery followed by adjuvant therapy based on pathologic findings⁴. Traditionally, RT has been recommended for patients with advanced local disease (T3-4), advanced nodal disease (N2-3), or sometimes a combination of minor pathologic risk factors (lymphovascular invasion, perineural invasion, etc.)⁴⁻⁶. Two randomized studies have demonstrated the efficacy of including concurrent chemotherapy with adjuvant radiotherapy for patients with either positive margins or extracapsular extension for the sake of enhancing locoregional control and overall survival^{7,8}.

The currently accepted indications for radiotherapy were developed historically and presumed to include all patients at high risk of loco-regional failure. The usual management of early T1-2, N0-1 involves surgical resection followed by observation, with radiotherapy reserved as part of salvage multimodality therapy for recurrent cases after salvage surgical resection, as it is generally thought that in this population there is no significant detriment to salvage strategy^{9,10}. More recently, however, it has become clear that stage I and II oral cavity squamous cell cancers represent a heterogeneous group of patients, some of whom have a risk of loco-regional recurrence as high as 25% when treated with surgery alone¹¹⁻¹³. Likewise, the American Joint Committee on Cancer (AJCC) has recognized that small but deeply invasive tumors demonstrate aggressive biological behavior and has now incorporated depth of invasion into the 8th edition of the staging system¹⁴. Both increased depth of invasion and tumor thickness are associated with a worse prognosis^{15,16}.

It is uncertain whether early stage patients with pathologic features such as lymphovascular invasion, perineural invasion, and tumor depth ≥4mm who are at high risk of loco-regional recurrence yet do not meet strict criteria for adjuvant radiation therapy (nodal positivity, T3-4 disease, positive margin, or Extracapsular spread) can be observed and successfully salvaged with surgery followed by salvage radiation at time of recurrence. Here, we sought to determine if outcomes for patients with recurrent oral cavity squamous cell cancer treated with salvage surgery and radiation resemble patients that received adjuvant post-operative RT upfront.

MATERIALS AND METHODS

A waiver of informed consent was obtained from the Memorial Sloan-Kettering Cancer Center (MSKCC) institutional review board. The tumor registry was used to identify patients with a diagnosis of non-metastatic oral cavity squamous cell carcinoma (OCSCC) treated with post-operative radiation between December 1989 and April 2011.

Patient and Tumor Characteristics

Complete fiberoptic nasopharyngoscopy was performed during pretreatment evaluation. Since 1995, computed tomography (CT) and/or magnetic resonance imaging scans are obtained for pretreatment evaluation. Additional imaging included a plain radiograph, chest CT or positron emission tomography (PET). All patients were staged in accordance with the AJCC 7th staging edition. Resection of the primary tumor was performed in all patients, including a repeat resection at recurrence in the salvage cohort. Neck dissection was performed based on nodal spread risk and at the discretion of the surgeon.

Radiotherapy

Prior to 2004, most patients received 3D-conformal radiation; since 2004, routine practice has been to use IMRT. Details regarding radiation treatment planning, targets, total-dose, and fractionation specification have been previously described^{17,18}. For conventional RT, 3D conformal therapy entailed opposed laterals and an anteroposterior (AP) supraclavicular field. The median dose to the postoperative bed was 60Gy (range, 50–70Gy) at 2Gy per fraction. For the anterior low-neck field, the dose was 50–50.4Gy in 1.8 to 2Gy per fraction.

Chemotherapy

Systemic therapy was administered for pathologic high-risk features including positive margins/gross residual disease and/or extracapsular extension. Most patients received cisplatin therapy, delivered at a dose of 100 mg/m² q3wks or weekly at 30–40 mg/m². In patients with renal toxicity, carboplatin and 5-fluorouracil was used. Alternatively, cetuximab was given with a loading dose prior to RT followed by 250mg/m² weekly.

Follow-up

Patients were evaluated every 2–3 months for the first 2 years after RT and every 4–6 months thereafter. CT, MRI, and/or PET scans were performed every 2–4 months. Chest radiographs and/or CT chest performed annually. If there was an area suspicious for recurrence, confirmatory biopsy was performed unless there was clear evidence of metastatic disease radiographically.

Statistical analysis

Kaplan-Meier method was used to estimate overall survival (OS), and log-rank test was used to compare OS curves. Gray's method was used to estimate cumulative incidence of local failure (LF), locoregional failure (LRF), and distant metastasis. Gray's test was employed to compare the cumulative incidence curves.

Since the salvage RT cohort was not treated at the baseline as with the adjuvant RT cohort, we applied a landmark analysis to reduce immortal time bias¹⁹. To compare adjuvant versus salvage RT cohorts, all survival endpoints were calculated 12 months post initial surgery (median time from initial surgery to recurrence for salvage RT was 9 months). Patient and clinical characteristics were compared between the two groups using Fisher's exact test. OS was analyzed using Cox proportional hazards regression model. LF, LRF, and distant metastasis were analyzed using Fine and Gray competing risks regression model, and death without event was a competing risk. Factors with a $p < 0.05$ on univariate analysis and type of RT were included in multivariate analysis. Statistical analyses were performed using SAS version 9.4 (SAS institute, Cary, NC) and R version 3.1.2 and the package "cmprsk". All statistical tests were two-sided and a $p < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

Patient characteristics at initial presentation for the adjuvant and salvage cohorts are listed in Table 1. There were no significant differences in the two treatment cohorts in terms of clinical characteristics by age, sex, smoking history, alcohol consumption and risk factors. The adjuvant cohort had more advanced T stage at diagnosis, T1: 23% vs 66%; T2: 34% vs 23%; T3: 9% vs 3%; T4: 34% vs 2% ($p < 0.0001$). The adjuvant cohort also had more locally advanced N stage at diagnosis, N0: 33% vs 93%; N1: 25% vs 2%; N2: 41% vs 3%, N3: 1% vs 0% ($p < 0.0001$). The difference in T and N stages between the two cohorts is expected given indications for adjuvant therapy. Primary tumor subsites in salvage group: oral tongue 68, floor of mouth 17, gingiva 16, buccal mucosa 12, other 11. In the adjuvant cohort, 24% received chemotherapy and/or biological agents. Of the patients who received chemotherapy, 65% received platinum-based treatment. Of those receiving non-platinum regimens, 44% of patients received cetuximab. The salvage group was observed at baseline and thus no patients received systemic therapy. Fisher's test could not be reliably performed on all pathologic variables secondary to missing data in the salvage cohort.

Adjuvant Cohort: Disease Control and Overall Survival

The median follow-up for survivors was 78 months (range, 3–281) from date of initial surgery²⁰. Primary tumor subsites: oral tongue 147, floor of mouth 46, gingiva 28, buccal mucosa 24, retromolar trigone 17, other 39. AJCC 7th edition stage distribution: I (6%), II (12%), III (24%), IV (57%). Following surgery, positive or close margins (≤ 1 mm) remained in 119 (39%), depth of invasion > 4 mm in 214 (71%), ECE in 82 (27%), and perineural invasion in 64 (21%). Adjuvant RT was delivered as 3DCRT ($n=144$, 48%) or IMRT ($n=154$, 51%).

The cumulative incidence of LF at 2 and 5 years was 14% and 20% respectively. The median time to LRF for the 83 patients who experienced loco-regional failure was 9.6 months from initial surgery (range 2.2 – 158 months). The cumulative incidence of LRF rates at 2 and 5 years were 21% and 27% (Fig. 1a). On univariate analysis, margin status was significantly associated with LRF ($p < 0.0001$), with a cumulative incidence of 17% LRF at 5 years for those with negative margins versus 42% for close or positive margins (Fig. 1b). The mode of

radiotherapy delivery (IMRT vs. conventional) was not significantly associated with LRF ($p=0.64$). Other factors associated with LRF, on univariate analysis included no daily alcohol use ($p=0.04$), higher N stage ($p=0.002$), and close ($p<0.0001$) or positive ($p=0.01$) surgical margins. On multivariate analysis, higher N stage (HR 1.84, 95% CI 1.2–2.82, $p=0.0005$), no daily alcohol use (HR 1.92, 95% CI 1.16–3.23, $p=0.01$), close and positive surgical margins (vs. negative margins respectively, HR 3.16, 95% CI 1.91–5.22, $p<0.0001$; HR 2.14, 95% CI 1.20–3.83, $p=0.01$) were predictors of LRF.

An exploratory multivariate analysis revealed that higher T stage and ECE were independently associated with a greater risk of distant metastasis using available ECE data. The median OS of the adjuvant cohort was 7.24 years. The 2, 5, and 10-year OS was 70%, 57%, and 39% respectively.

Disease Control: Salvage and Upfront Adjuvant RT

For the landmark analysis examining adjuvant and salvage cohorts, Fine and Gray competing risks multivariate analysis model showed that after adjusting for status of alcohol consumption and T stage, patients who received salvage RT experienced marginally poorer LC as compared to adjuvant cohort (HR 1.35, 95% CI 0.99–1.84, $p=0.06$). Multivariate analysis of loco-regional failure also showed that patients who received salvage therapy had increasing LRF (HR 1.56, 95% CI 1.18–2.06, $p=0.002$). On multivariate analysis, salvage therapy was also significantly associated with distant metastasis (HR 1.53, 95% CI 1.08–2.17, $p=0.02$).

Further analysis was performed with the exclusion of locally advanced patients from the salvage cohort, specifically T3–T4 and N2 disease. After adjusting for T stage on MVA, salvage RT treatment selection for early stage OCSCC continued to experience increasing LRF (HR 1.65, 95% CI 1.12–2.43, $p=0.01$) and distant metastasis as compared to adjuvant RT (HR 1.77, 95% CI 1.11–2.82, $p=0.02$).

Overall Survival: Salvage and Upfront Adjuvant RT

The median follow-up from the landmark 12 months post initial surgery for survivors in the combined cohort was 77 months (range, 0.22–317.2 months). On univariate analysis, older patients (≥ 45 vs. <45 year, HR 0.56, 95% CI 0.35–0.90, $p=0.02$) experienced an increase in OS while T4 disease had shorter OS as compared to stage T1 (HR 1.50, 95% CI 1.01–2.22, $p=0.04$, Table 2). On multivariate analysis, Age (≥ 45 vs. <45 year, HR 0.54, 95% CI 0.34–0.87, $p=0.01$) and T stage (T4 vs. T1, HR 2.28, 95% CI 1.41–3.68, $p=0.0008$) were independent prognostic factors for OS. Multivariate analysis also showed that treatment selection significantly impacted survival after adjusting for age and T stage, with salvage RT patients experiencing poorer OS as compared to adjuvant RT (HR 1.84, 95% CI 1.26–2.70, $p=0.002$; Table 2). Adjusted overall survival curves for the two cohorts took into account age, T-stage, and cohort estimated a 2-year OS of 83% vs 59% and a 5-year OS of 72% vs 46% between adjuvant and salvage cohorts (Fig. 2).

Additional analysis was performed with the exclusion of locally advanced patients in the salvage cohort, specifically T3–T4 and N2 disease. After adjusting for T stage on MVA,

salvage RT treatment selection for early stage OCSCC continued to experience significantly poorer OS as compared to adjuvant RT (HR 1.48, 95% CI 1.002–2.19, $p=0.049$).

Predicted loco-regional control and AJCC stage Salvage cohort

We utilized the nomogram developed by Wang et al to assess the predicted 5-year locoregional control rates for our salvage cohort (Fig 3a)²¹. In addition, we restaged the salvage cohort according to the AJCC 8th edition. There was a shift to more advanced T stage when utilizing the new AJCC 8th edition staging. The incidence of T1 tumors decreased by 13%, while both T2 and T3 tumors increased by 8% and 9% respectively (Fig 3b).

DISCUSSION

We examined the outcomes of OCSCC patients that were observed, subsequently recurred, and then received salvage surgery followed by radiotherapy versus those of patients with OCSCC treated with upfront adjuvant radiotherapy. Notably, we found poor outcomes for patients that recurred after surgery alone and who received RT following salvage surgery at recurrence. We performed the analysis both with and without the inclusion of locally advanced patients in the salvage cohort. and salvage treatment selection was inferior to adjuvant RT in terms of overall survival, LRC, and distant metastasis for early stage OCSCC patients. Our findings contradict recent studies suggesting salvage therapy in non-irradiated patients is fair and similar to those with de-novo stage III/IV disease^{9,10}. In fact, our findings suggest that outcomes are worse for early stage non-irradiated patients when the cohorts are directly compared to each other. Studies utilizing national pattern of care databases suggest that the 5 year survival of early stage OCSCC is in the range of 70% and loco-regional failure rates range between 10–25%^{22–25}, suggesting moderate clinical heterogeneity in this group of patients.

Although single institution and multi-institutional studies demonstrate improved outcomes in early stage patients, they also continue to show heterogeneity in outcomes. In a study of 148 patients with surgically resected pT1-2cN0 OCSCC with negative margins, the 3yr RFS was 89.7%. However, multivariate analysis revealed that lymphovascular invasion was associated with a 50% recurrence rate (OR=10.7, $p=0.007$)¹¹. Ganly et al., described a multi-institutional cohort of 164 patients with pT1-2N0 oral tongue SCC who underwent partial glossectomy and ipsilateral neck dissection without postoperative RT¹⁵. While the 5 year overall local recurrence free survival was 89%, the regional recurrence varied significantly by tumor depth. Patients whose tumors had a depth of invasion <4mm had a 5.7% rate of recurrence, while those whose tumors had depth ≥4mm had 24%¹⁵. Moreover, patients who developed neck recurrence had significantly poorer disease-specific survival compared to those who did not 33% vs. 97% ($p<0.0001$). In one of the largest series by Liao et al, 457 patients with pT1-2N0 OCSCC disease were examined after radical surgery. Poor differentiation and tumor depth of 4mm or greater resulted in 5-year LC, neck control, and DFS of 80%, 58%, and 50% respectively^{13,26}.

Both institutional and national database studies suggest a subset of early stage OCSCC patients have a moderate risk of LRF. The 5-year outcomes of patients with recurrent

OCSCC are in the range of 25% to 48%^{27,28}. In a recently published retrospective study of recurrent OCSCC, 78 patients treated with salvage multimodality therapy (surgery and radiation) had a high 5yr survival of 56%, possibly due to the exclusion of patients unable to be surgically salvaged⁹.

For early T1/T2 OCSCC node negative disease, there are occult neck metastases upwards of 30%²⁹. In a randomized study by D'Cruz et al, there was a DFS (3yr 69.5% vs 45.9% $p<0.001$) and OS benefit (3yr OS 80% vs 67.5% $p=0.01$) with elective neck dissection for node negative T1/T2 OCSCC²². Delaying loco-regional therapy for patients with high recurrence risk in early OCSCC, whether surgery or radiation therapy, appears to be detrimental. Similarly, in our study, even though the adjuvant cohort had more locally advanced disease than the salvage cohort, on both univariate analysis as well as on multivariate analysis, the selection of salvage therapy was associated with significantly lower rates of LRC and OS as well as higher rates of distant metastasis, highlighting the importance of adequate upfront loco-regional therapy.

The poor outcomes in a subset of early stage OCSCC patients that recur suggest that there is an urgent need for a randomized study to try and address if more aggressive loco-regional therapy in a high risk subset could improve oncologic outcomes. Efforts to identify the added value of post-operative RT are underway, with an ongoing European trial examining adjuvant RT in pT1-2N1 OCSCC and oropharyngeal cancers (negative margins)³⁰. However, our data which demonstrates very poor outcomes in primarily T1-2N0 OCSCC patients following recurrence, along with others^{11,13,15,22} suggests that studies are needed in T1-2N0 patients to elucidate if adjuvant radiotherapy improves oncologic outcomes. A better understanding of the genomic heterogeneity of OCSCC could also help develop an optimal tailored therapeutic strategy³¹.

Along these lines, a recent analysis of 1000 locally advanced HNSCC patients treated with IMRT as part of definitive therapy demonstrated that OCSCC tumors demonstrate the highest risk of LRF compared to other HNSCC sub-sites, most of which are isolated LRFs, despite many OCSCC patients receiving trimodality therapy³². These data highlight the challenge of achieving locoregional control, even with modern treatment modalities.

Postoperative radiation, however, is not without side effects and carries both acute and late toxicities. In the study by Cooper et al, the incidence of acute grade 3 toxicities was 34% and 20.5% of patients developed grade 3–5 late toxicity. At 5yrs, grade 3–4 late toxicity was 9.3%^{7,33}. The most common late toxicity remains dry mouth³⁴. Postoperative IMRT studies, which utilize generous target volumes, have late grade 3 event rate of 9%³⁵. Feeding tube placement during post-operative RT for OCSCC are in the range of 14–40%^{36,37}. Early stage OCSCC should have lower rates of feeding tube placement as there is less functional deficit from surgery and radiation³⁶. It is outside the scope of our current study to formally examine toxicity however these associated side effects of radiotherapy need to be carefully balanced with oncologic benefit to help identify appropriate patients for adjuvant therapy.

In almost all cancers adjuvant radiotherapy reduces the relative risk of loco-regional recurrence between 50–75%^{38–42}. Even in cases where the absolute incidence of loco-

regional recurrence is low, randomized studies demonstrate consistent reduction in LRR^{39,43}. Nomograms have been developed to identify early stage patients at high loco-regional risk in OCSCC, however they do not include depth of invasion, lvi, or pni, and appear to under-estimate the benefit of adjuvant radiotherapy due to selection bias used to construct the nomogram²¹. For example, although our data suggests chemotherapy is associated with increased distant metastasis and indicative of a selection bias for patients receiving chemotherapy. Similarly, retrospective data trying to estimate the benefit of adjuvant radiotherapy will underestimate benefits due to similar bias. These findings, again, highlight the importance of addressing this question in a randomized manner.

Our study is limited by its retrospective nature and associated biases. Comparative analyses performed on adjuvant and salvage RT is limited by inherent bias: the adjuvant RT cohort is disease free but has the potential to develop recurrence whereas the salvage RT cohort has already suffered a recurrence, and although earlier stage, may have biologically more aggressive disease. Irrespective of this, our data suggests that preventing recurrence is associated with improved outcomes. Updates for the AJCC 8th edition-staging appear to be promising in terms of risk group stratification. Unfortunately, pathologic features including tumor depth of invasion were not reported for all patients in the salvage cohort at initial presentation and statistical testing could not be performed on all pathologic features. Moreover, AJCC 8th edition restaging may have upstaged more patients in the salvage cohort. It is possible that more patients would have received adjuvant therapy under the new classification system accurately reflecting their prognosis and recurrence risk. In addition, the patients treated with salvage RT have lead time bias after initial surgery when compared to patients that receive adjuvant RT as they have yet to declare themselves as belonging to the salvage group. We accounted for this by performing a landmark analysis from 12 months post initial surgery to reduce immortal time bias.

CONCLUSION

We report on a large population of OCSCC treated with postoperative radiation. Early stage OCSCC patients who are observed and experience recurrence requiring salvage therapy (surgery and radiotherapy) have worse outcomes than locally advanced patients receiving upfront adjuvant radiotherapy. Prospective randomized studies are needed to identify high-risk subset of early stage OCSCC comparing adjuvant RT versus observation followed by salvage surgery and RT at recurrence.

Acknowledgments

Funding support provided by MSKCC Cancer Center Support Grant P30 CA008748-50.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians. 2017; 67(1):7–30. [PubMed: 28055103]
2. Ganly I, Patel S, Shah J. Early stage squamous cell cancer of the oral tongue--clinicopathologic features affecting outcome. Cancer. 2012; 118(1):101–111. [PubMed: 21717431]
3. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral oncology. 2009; 45(4–5):309–316. [PubMed: 18804401]

4. 2.2016 NGV. Cancer of the Oral Cavity. 2017.
5. Studer G, Furrer K, Davis BJ, et al. Postoperative IMRT in head and neck cancer. *Radiation oncology*. 2006; 1:40. [PubMed: 17052346]
6. Fan KH, Wang HM, Kang CJ, et al. Treatment results of postoperative radiotherapy on squamous cell carcinoma of the oral cavity: coexistence of multiple minor risk factors results in higher recurrence rates. *International journal of radiation oncology, biology, physics*. 2010; 77(4):1024–1029.
7. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *The New England journal of medicine*. 2004; 350(19):1937–1944. [PubMed: 15128893]
8. Bernier J, Dommene C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *The New England journal of medicine*. 2004; 350(19):1945–1952. [PubMed: 15128894]
9. Quinlan-Davidson SR, Morrison WH, Myers JN, et al. Recurrent oral cavity cancer: Patterns of failure after salvage multimodality therapy. *Head & neck*. 2017; 39(4):633–638. [PubMed: 28006086]
10. Tam S, Araslanova R, Low TH, et al. Estimating Survival After Salvage Surgery for Recurrent Oral Cavity Cancer. *JAMA otolaryngology-- head & neck surgery*. 2017; 143(7):685–690. [PubMed: 28448645]
11. Huang TY, Hsu LP, Wen YH, et al. Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. *Oral oncology*. 2010; 46(1):49–55. [PubMed: 20005769]
12. Langendijk JA, Slotman BJ, van der Waal I, Doornaert P, Berkof J, Leemans CR. Risk-group definition by recursive partitioning analysis of patients with squamous cell head and neck carcinoma treated with surgery and postoperative radiotherapy. *Cancer*. 2005; 104(7):1408–1417. [PubMed: 16130134]
13. Liao CT, Lin CY, Fan KH, et al. Identification of a high-risk group among patients with oral cavity squamous cell carcinoma and pT1-2N0 disease. *International journal of radiation oncology, biology, physics*. 2012; 82(1):284–290.
14. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. *CA: a cancer journal for clinicians*. 2017; 67(2):122–137. [PubMed: 28128848]
15. Ganly I, Goldstein D, Carlson DL, et al. Long-term regional control and survival in patients with “low-risk,” early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. *Cancer*. 2013; 119(6):1168–1176. [PubMed: 23184439]
16. Spiro RH, Huvos AG, Wong GY, Spiro JD, Gnecco CA, Strong EW. Predictive value of tumor thickness in squamous carcinoma confined to the tongue and floor of the mouth. *American journal of surgery*. 1986; 152(4):345–350. [PubMed: 3766861]
17. Dutta PR, Riaz N, McBride S, et al. Postoperative PET/CT and target delineation before adjuvant radiotherapy in patients with oral cavity squamous cell carcinoma. *Head & neck*. 2016; 38(Suppl 1):E1285–1293. [PubMed: 26335113]
18. Gomez DR, Zhung JE, Gomez J, et al. Intensity-modulated radiotherapy in postoperative treatment of oral cavity cancers. *International journal of radiation oncology, biology, physics*. 2009; 73(4): 1096–1103.
19. Ascierto PA, Long GV. Progression-free survival landmark analysis: a critical endpoint in melanoma clinical trials. *The Lancet Oncology*. 2016; 17(8):1037–1039. [PubMed: 27324281]
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958; 53(282):457–481.
21. Wang SJ, Patel SG, Shah JP, et al. An oral cavity carcinoma nomogram to predict benefit of adjuvant radiotherapy. *JAMA otolaryngology-- head & neck surgery*. 2013; 139(6):554–559. [PubMed: 23680917]
22. D'Cruz AK, Vaish R, Kapre N, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. *The New England journal of medicine*. 2015; 373(6):521–529. [PubMed: 26027881]

23. Rusthoven K, Ballonoff A, Raben D, Chen C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. *Cancer*. 2008; 112(2):345–351. [PubMed: 18041071]
24. Luryi AL, Chen MM, Mehra S, Roman SA, Sosa JA, Judson BL. Treatment Factors Associated With Survival in Early-Stage Oral Cavity Cancer: Analysis of 6830 Cases From the National Cancer Data Base. *JAMA otolaryngology-- head & neck surgery*. 2015; 141(7):593–598. [PubMed: 25974757]
25. Lydiatt DD, Robbins KT, Byers RM, Wolf PF. Treatment of stage I and II oral tongue cancer. *Head & neck*. 1993; 15(4):308–312. [PubMed: 8360052]
26. Chen MM, Roman SA, Yarbrough WG, Burtneess BA, Sosa JA, Judson BL. Trends and variations in the use of adjuvant therapy for patients with head and neck cancer. *Cancer*. 2014; 120(21):3353–3360. [PubMed: 25042524]
27. Studer G, Brown M, Bredell M, et al. Follow up after IMRT in oral cavity cancer: update. *Radiation oncology*. 2012; 7:84. [PubMed: 22686297]
28. Schwartz GJ, Mehta RH, Wenig BL, Shaligram C, Portugal LG. Salvage treatment for recurrent squamous cell carcinoma of the oral cavity. *Head & neck*. 2000; 22(1):34–41. [PubMed: 10585603]
29. Peng KA, Chu AC, Lai C, et al. Is there a role for neck dissection in T1 oral tongue squamous cell carcinoma? The UCLA experience. *American journal of otolaryngology*. 2014; 35(6):741–746. [PubMed: 25091179]
30. Moergel M, Jahn-Eimermacher A, Krummenauer F, et al. Effectiveness of adjuvant radiotherapy in patients with oropharyngeal and floor of mouth squamous cell carcinoma and concomitant histological verification of singular ipsilateral cervical lymph node metastasis (pN1-state)--a prospective multicenter randomized controlled clinical trial using a comprehensive cohort design. *Trials*. 2009; 10:118. [PubMed: 20028566]
31. Riaz N, Morris LG, Lee W, Chan TA. Unraveling the molecular genetics of head and neck cancer through genome-wide approaches. *Genes & diseases*. 2014; 1(1):75–86. [PubMed: 25642447]
32. Leeman JE, Li JG, Pei X, et al. Patterns of Treatment Failure and Postrecurrence Outcomes Among Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma After Chemoradiotherapy Using Modern Radiation Techniques. *JAMA oncology*. 2017
33. Cooper JS, Zhang Q, Pajak TF, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *International journal of radiation oncology, biology, physics*. 2012; 84(5):1198–1205.
34. Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2008; 26(22):3770–3776. [PubMed: 18669465]
35. Geretschlager A, Bojaxhiu B, Crowe S, et al. Outcome and patterns of failure after postoperative intensity modulated radiotherapy for locally advanced or high-risk oral cavity squamous cell carcinoma. *Radiation oncology*. 2012; 7:175. [PubMed: 23088283]
36. Mangar S, Slevin N, Mais K, Sykes A. Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. *Radiation oncology: journal of the European Society for Therapeutic Radiology and Oncology*. 2006; 78(2):152–158. [PubMed: 16466819]
37. Sher DJ, Thotakura V, Balboni TA, et al. Treatment of oral cavity squamous cell carcinoma with adjuvant or definitive intensity-modulated radiation therapy. *International journal of radiation oncology, biology, physics*. 2011; 81(4):e215–222.
38. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet*. 2000; 355(9217):1757–1770. [PubMed: 10832826]
39. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. *International journal of radiation oncology, biology, physics*. 2005; 63(3):834–838.

40. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *International journal of radiation oncology, biology, physics*. 2006; 65(1):169–176.
41. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *European urology*. 2014; 66(2):243–250. [PubMed: 24680359]
42. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *The Lancet Oncology*. 2012; 13(6):589–597. [PubMed: 22575589]
43. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005; 366(9503):2087–2106. [PubMed: 16360786]

Figure 1. Outcomes in the adjuvant radiation cohort

(A) 5-year cumulative incidence curve of LRF after surgery for the adjuvant cohort. The 2- and 5- year LRF was 21% and 27%, respectively.

(B) 5-year cumulative incidence curves of LRF by margin status for the adjuvant cohort. The 5-year LRF for negative margin was 17% vs 42% for close or positive margins, $p < 0.0001$.

Figure 2.

Comparison of overall survival between recurrent oral cavity cancer treated with salvage surgery and radiation versus adjuvant RT. Adjusted overall survival curves stratified by cohort are derived from the multivariate analysis Cox proportional hazards regression model.

Figure 3. Modern tools to examine the recurrence risk of the salvage cohort at initial presentation: Nomogram and AJCC 8th edition

(A) Salvage cohort and predicted 5year locoregional control with surgery versus surgery and adjuvant RT using the oral cavity nomogram²¹.

(B) Salvage cohort and AJCC restaging from the 7th to the 8th edition.

Table 1

Baseline Patient Characteristics at initial surgery between the adjuvant RT and salvage surgery and RT patient cohorts using Fisher's exact test (N=425). Fisher's test was not reported for all patient characteristics secondary to missing data.

	Adjuvant RT N=301 (%)	Salvage RT N=124 (%)	p-value
Age	61	60	
<45	252(84)	104(84)	1.00
45	49(16)	20(16)	
Sex			1.00
Male	175(58)	77(62)	
Female	126(42)	47(38)	
Smoking			1.00
10 pack*year	156(52)	66(53)	
>10 pack*year	137(46)	58(47)	
Alcohol consumption			0.2
No	200(66)	92(74)	
Daily or more	97(32)	32(26)	
T stage			<0.0001
1	70(23)	82(66)	
2	102(34)	29(23)	
3	26(9)	4(3)	
4	103(34)	2(2)	
N stage			<0.0001
0	100(33)	115(93)	
1	75(25)	3(2)	
2	124(41)	4(3)	
3	2(1)	0(0)	
Stage Grouping			
I	20(7)	79(64)	<0.0001
II	36(12)	25(20)	
III	73(24)	7(6)	
IV	172(57)	6(5)	
Margins			NA
Negative	179(59)	57(46)	
Close	64(21)	30(24)	
Positive	55(18)	0(0)	
PNI			NA
No	118(39)	41(33)	
Yes	129(43)	14(11)	

	Adjuvant RT N=301 (%)	Salvage RT N=124 (%)	p-value
PVI/LVSI			NA
No	188(62)	50(40)	
Yes	64(21)	7(6)	
ECE			NA
No	165(55)	34(27)	
Yes	82(27)	2(2)	
Depth of Invasion median, Inter quartile range (IQR)	12(8,17)	6(4,9)	NA
Chemotherapy			NA
No	229(76)		
Yes	72(24)		

PNI, Perineural invasion; PVI, perivascular invasion; LVSI, lympho-vascular space invasion; ECE, extracapsular extension; NA, Not available; UVA, univariate analysis; MVA, multivariate analysis.

Table 2

Univariate and multivariate analysis of overall survival for the adjuvant and salvage* radiation groups.

	UVA HR (95% CI)	p-value	MVA HR (95%CI)	p-value
Age				
<45	1.00		1.00	
45	0.56 (0.35–0.90)	0.02	0.54 (0.34–0.87)	0.01
Sex				
Male	1.00			
Female	0.99 (0.73–1.34)	0.95		
Smoking pack year				
10	1.00			
>10	1.29 (0.95–1.73)	0.10		
Alcohol				
No	1.00			
Daily	1.13 (0.83–1.54)	0.43		
T stage				
1	1.00		1.00	
2	0.94 (0.66–1.34)	0.71	1.22 (0.83–1.80)	0.31
3	1.03 (0.56–1.90)	0.93	1.60 (0.82–3.12)	0.17
4	1.50 (1.01–2.22)	0.04	2.28 (1.41–3.68)	0.0008
N stage				
0	1.00			
1	0.98 (0.67–1.44)	0.92		
2/3	0.98 (0.66–1.44)	0.90		
Treatment				
Adjuvant	1.00		1.00	
Salvage	1.26 (0.93–1.70)	0.14	1.84 (1.26–2.70)	0.002

* all of the patients in the salvage radiation group received salvage surgery prior to radiation.