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Authors

Lok, Benjamin H
Chin, Christine
Riaz, Nadeem
et al.

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Irradiation for locoregionally recurrent, never-irradiated oral cavity cancers

Benjamin H. Lok, MD[1], **Christine Chin, BS**[1], **Nadeem Riaz, MD**[1], **Felix Ho, MD**[1], **Man Hu, MD**[1], **Julian C. Hong, MS**[2], **Weiji Shi, MS**[3], **Zhigang Zhang, PhD**[3], **Eric Sherman, MD**[4], **Richard J. Wong, MD**[5], **Luc G. Morris, MD**[5], **Ian Ganly, MD, PhD**[5], **Suzanne L. Wolden, MD**[1], **Shyam S. Rao, MD, PhD**[1], and **Nancy Y. Lee, MD**[1,*]

[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York

[2]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California

[3]Department of Epidemiology and Biostatistics, Memorial Sloan–Kettering Cancer Center, New York, New York

[4]Department of Medicine, Head and Neck Oncology Service, Memorial Sloan–Kettering Cancer Center, New York, New York

[5]Department of Surgery, Head and Neck Service, Memorial Sloan–Kettering Cancer Center, New York, New York

Abstract

Background—The purpose of this study was to report the clinical outcomes and related prognostic factors of patients who underwent radiotherapy (RT) for the treatment of recurrent, never-irradiated oral cavity cancer (recurrent OCC).

Methods—The records of consecutive patients with nonmetastatic recurrent OCC who presented to and were treated with RT at our institution between 1989 and 2011 were reviewed. The Kaplan–Meier method was used to calculate overall survival (OS). The cumulative incidences of disease-specific death, local failure, regional failure, and distant metastasis were calculated with death as a competing risk.

Results—One hundred twenty-three patients were identified. Median follow-up for living patients was 54 months and 16 months for all patients. Ninety-one patients had salvage surgery followed by adjuvant RT. Definitive RT was utilized in the remaining 32 patients. The 5-year OS was 40%. The 5-year cumulative incidence of disease-specific death, local failure, regional failure, and distant metastasis was 55%, 34%, 22%, and 20%, respectively. Recurrent T classification and lack of salvage surgery were independently associated with worse disease-specific death and decreased OS, respectively. Subset analysis of patients who underwent salvage surgery demonstrated that age, recurrent T classification, and perineural invasion (PNI) were

[*]**Corresponding author:** N. Y. Lee, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065. Leen2@mskcc.org.

Benjamin H. Lok and Christine Chin contributed equally to this work.

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independently associated with decreased OS; recurrent T classification and thicker tumors were independently associated with worse disease-specific death; and positive/close margins and primary T classification were independently associated with increased local failure.

Conclusion—In this group of patients with recurrent OCC, clinical outcomes were similar or improved when compared with other recurrent OCC-specific reports. In the salvage surgery subset, tumor thickness and PNI are recurrent pathologic features associated with outcomes that were only previously demonstrated in studies of primary disease. Because of the relatively worse outcomes in patients receiving definitive or adjuvant RT for recurrent OCC, we advocate for the appropriate use of postoperative RT in the initial management of oral cavity cancers.

Keywords

oral cavity; recurrent; radiotherapy; surgery; clinical outcomes

INTRODUCTION

It is estimated that, in the United States, 26,740 people will be diagnosed with and 5520 people will die of oral cavity cancer (OCC).[1] Compared with other head and neck subsites, the 5-year locoregional recurrence rates in OCC are substantially greater and reported to be as high as 50%.[2–4]

Treatment of recurrent OCC is typically managed by salvage surgery with adjuvant radiotherapy (RT) and/or chemotherapy. When a surgical approach is not possible, definitive RT with or without chemotherapy is the preferred option.[5] Treatment failure after salvage therapy is high, with the greatest disease-free survival rates occurring in patients amenable to salvage surgery.[5,6] Because of the high risk of future recurrence and the generally more advanced presentation of disease, RT has been used extensively as adjuvant therapy or definitively for patients with unresectable tumors or inability to tolerate salvage surgery.

There are limited reports examining the role of RT in the management of recurrent OCC.[6,7] RT treatment outcomes and prognostic factors for recurrent disease in this particular subsite are relatively understudied and were the purpose of this study. We sought to report the results of RT in patients with recurrent OCC with respect to overall survival (OS), disease-specific death, and rates of local, regional, and distant metastatic failure. We also examined various factors that may be associated with the aforementioned clinical outcomes, such as disease stage, surgical margin status, tumor thickness, perineural invasion (PNI), extracapsular extension (ECE), and lymphovascular invasion (LVI), among several others.

MATERIALS AND METHODS

After obtaining a waiver of documentation of consent and approval from our institutional review board, we retrospectively reviewed the records of 123 consecutive patients who presented to our institution between December 1989 and April 2011 with a histologically proven diagnosis of recurrent nonmetastatic oral cavity squamous cell carcinoma and were subsequently referred to the Department of Radiation Oncology for RT and had never received radiation for the management of their disease.

Recurrent OCCs were defined as any local or regional recurrence of disease after primary definitive surgery. Nineteen patients (15%) presented with recurrent disease greater than 5 years from their original diagnosis. At presentation, a complete history and physical, laryngoscopic examination, and imaging studies (eg, chest X-ray, CT, and/or positron emission tomography) were performed. Pathologic specimens were reviewed for each patient at our center to confirm the diagnosis.

The management of recurrent OCC was determined in a multidisciplinary discussion among surgical, medical, and radiation oncologists. Our institutional policy is to treat recurrent OCC surgically when possible. For patients who underwent salvage surgery for their recurrent disease before RT, at the time of microscopic examination of the excision specimens, surgical margins were defined as positive if tumor cells were extending to the margin and close when a tumor was visualized ≤1 mm from any surgical margin.

Adjuvant RT was generally given for patients who received no prior RT. Besides presenting with recurrent disease, additional indications for postoperative radiation were the presence of high-risk features, including T3 to T4 classification, positive or close surgical margins, PNI, lymphovascular invasion, ECE, or nodal involvement. Definitive RT was used for salvage for patients who refused surgical salvage, presented with tumors considered surgically unresectable, or were unfit for general anesthesia.

RT details regarding target delineation, dose specifications, and guidelines used at our center have been previously described in detail for both conventional RT[8] and intensity-modulated radiation therapy (IMRT) approaches.[4] In brief, the median prescription dose delivered to the postoperative bed was 63 Gray (Gy) for postoperative patients and 70 Gy for definitively treated patients. For IMRT patients, treatment fields encompassed areas of gross disease with the planning target volume including a 0.3- to 0.5-cm margin around the gross tumor volume. The high-risk clinical target volume included the preoperative gross disease and the postoperative tumor bed at the primary site, along with any nodal regions with disease involvement. The planning target volume margin for high-risk clinical target volume was generally 0.5 cm.

Chemotherapy was given to patients who were at high risk of distant metastatic failure at the discretion of the treatment team. In general, chemotherapy was delivered for patients with positive surgical margins, pathologic evidence of ECE or substantial nodal disease, LVI, and PNI.[9]

Acute and late toxicities were graded using the Common Terminology Criteria for Adverse Events 3.0 at each patient encounter during treatment and at each follow-up visit.

Endpoints and statistical analysis

All endpoints were calculated from the initiation of RT. OS was estimated using the Kaplan–Meier method and was compared in univariate analysis using the log-rank test for discrete variables or Cox proportional hazards regression model for continuous variables. Stepwise selection was then used to construct multivariate Cox models. The cumulative incidences of disease-specific death, local failure, regional failure, and distant metastasis were calculated

with death without event as a competing risk. univariate analysis of these outcomes was performed using Gray's nonparametrical or parametrical competing risks (the latter for continuous variables) and stepwise multivariate parametrical competing risks method. In addition, for variables >2 categories, post hoc comparisons were conducted if the global test was significant on univariate analysis. The Benjamini and Hochberg False Discovery Rate controlling procedure was used to correct for multiple testing and reported as adjusted p values.[10] Factors with adjusted p values of <.1 on univariate analysis were considered candidates for the multivariate analysis. A subset analysis of patients who underwent salvage surgery was performed to determine the association of recurrent histologic features with patient outcomes. The SAS 9.2 (SAS Institute, Cary, NC) and R 2.9.2 software packages were used for statistical analysis.

RESULTS

Patient and tumor characteristics are summarized in Tables 1 and 2. The median follow-up among survivors was 54.8 months and for all patients was 16.33 months (range, 3.2–260.9 months). One hundred one patients (81%) presented with recurrent American Joint Committee on Cancer (AJCC) stage III or nonmetastatic stage IV disease.

Initial treatment

At presentation of primary disease, all patients underwent surgical resection without adjuvant RT (Table 2). Primary surgery entailed local resection only in 67 patients (54%) and in combination with neck dissection in an additional 56 patients (46%). The dates of primary surgery ranged from September 1975 to July 2010 with the vast majority of patients (120; 97%) undergoing primary surgery after 1985 when CT was available for regional staging by radiologic imaging. Sixty-six patients (53%) underwent initial surgical treatment at outside hospitals, with the remaining 46 patients (47%) being treated initially at our institution. One hundred thirteen patients (91%) were pathologically or clinically node negative at the time of first presentation (Table 2).

Recurrent treatment

Surgery—The surgical management of patients presenting with recurrent disease is summarized in Table 2. Ninety-one patients (73%) underwent salvage surgery, 6 patients (5%) had local resection only, 46 patients (37%) underwent local and regional surgical management, and 39 patients (31%) had neck salvage alone. All 91 patients received surgical management of their recurrent disease at our institution. Pathology reports identified 9 patients (10%) with positive margins and 19 patients (21%) with close surgical margins (≤1 mm) after salvage surgery.

Radiotherapy—All patients were radiation naive at the site(s) of recurrent disease and received RT for their recurrent disease at our institution. In patients treated by definitive RT, the median dose delivered was 70 Gy (range, 42.4–74 Gy). Eighty-four percent of patients received ≥64 Gy. The median dose in the postoperative setting was 63 Gy (range, 46–70.2 Gy). Seventy-seven percent of patients received between 60 and 63 Gy. Radiation was

delivered by IMRT to 55 patients (44%) with the remaining 69 patients (56%) receiving radiation through conventional RT methods.

Chemotherapy—Fifty-five patients (45%) received chemotherapy as part of their treatment of recurrent disease (Table 2), of which all were concurrent with RT. Cisplatin alone was the most common systemic agent of choice (34 patients; 62%), with a moderate number of patients receiving cetuximab alone (12 patients; 22%). The remaining 9 patients (16%) undergoing chemotherapy typically received carboplatin-based regimens (5 patients; 9%).

Recurrence and survival after treatment of recurrent disease

Please see Tables 3 and 4 for all prognostic factors analyzed in all patients as well as Tables 5 and 6 for all factors analyzed in patients who underwent salvage surgery.

Overall survival—The 5-year OS was 40% (95% confidence interval [CI]=30% to 49%) and 47% (95% CI=36% to 58%) for all patients and salvage surgery subset, respectively (Figures 1 and 2). For all patients, univariate analysis and post hoc pairwise comparison revealed that higher recurrent T classification, positive/close surgical margins, or not undergoing salvage surgery were significantly associated with worse OS (Table 3). Lack of salvage surgery (vs negative margin) remained the independent factor associated with worse OS on multivariate analysis (Table 4).

In patients who underwent salvage surgery, higher recurrent T classification, positive/close margin status, PNI, and thicker tumors were significantly associated with decreased OS on univariate analysis (Table 5). However, in the multivariate analysis model, older age, recurrent T classification, and PNI were found to be independently associated with worse OS (Table 6).

Disease-specific death—The 5-year disease-specific death was 55% (95% CI=45% to 64%; Figure 3) for all patients and 47% (95% CI=36% to 58%; Figure 4) in salvage surgery patients. Univariate analysis demonstrated that higher recurrent T classification and not undergoing salvage surgery (vs negative margins) were significantly associated with worse disease-specific death in all patients (Table 3). Higher recurrent T classification remained an independent factor associated with worse disease-specific death on multivariate analysis (Table 4).

In the salvage surgery subset, a trend toward worse disease-specific death was seen with higher recurrent T classification ($p = .091$) and greater tumor thickness ($p = .57$). These 2 factors were found to be independently associated with worse disease-specific death after multivariate analysis.

Local failure—The 5-year cumulative incidence of local failure was 34% (95% CI=26% to 43%; Supplemental Figure 1, online only) for all patients and 31% (95% CI=21% to 41%; Supplemental Figure 2, online only) in the surgical subset. Local failure occurred in 41 patients. From the start of RT, the median time to recurrence for these patients was 6.9 months (range, 2.2–87.8 months). Of patients with local failure, the tumor subsite was oral

tongue in 23 (56%), gingiva in 4 (10%), with the remaining subsites of hard palate, buccal mucosa, lip, floor of mouth in 3 independent patients each (7%). Twenty-six patients (76%) received postoperative RT, whereas 15 patients (37%) underwent definitive RT. Twenty-eight patients (44%) had presented with recurrent AJCC stage IVA or IVB disease.

In all patients, univariate competing risks analysis revealed that higher recurrent T classification, positive/close surgical margins, or not undergoing salvage surgery, were associated with increased rates of local failure (Table 3).

In patients who underwent salvage surgery, univariate analysis demonstrated recurrent T classification, positive/close margins, and primary T classification were associated with increased local failure (Table 5). After multivariate analysis, positive/close margins and initial T classification remained independently associated with greater local failure rates (Table 6).

Regional failure—The 5-year cumulative incidence of regional failure was 22% (95% CI=14% to 29%; Supplemental Figure 3, online only) for all patients and 22% (95% CI=13% to 31%; Supplemental Figure 4, online only) for the salvage surgery subset. Regional failure occurred in 26 patients. The median time to recurrence for them was 5.5 months from the initiation of RT (range, 0.6–75.8 months). The primary tumor was located in the oral tongue in 14 patients (56%), gingiva in 4 patients (16%), hard palate in 3 patients (12%), floor of mouth in 3 patients (12%), and buccal mucosa in 1 patient (4%). Twenty patients (80%) received postoperative adjuvant RT and the remaining 5 patients (20%) were treated definitively. Nineteen patients (76%) had presented with recurrent AJCC stage IVA or IVB disease. After multiple testing correction, no covariates were significantly associated with regional failure in all patients or the surgical subset (Tables 3 and 5).

Distant metastasis—The 5-year cumulative incidence of distant metastasis was 20% (95% CI=13% to 28%; Supplemental Figure 5, online only) in all patients and 20% (95% CI=11% to 28%; Supplemental Figure 6, online only) for patients who underwent salvage surgery. Twenty-seven patients had at least one distant metastasis during the follow-up period. The median time to distant recurrence for these patients was 7.2 months (range, 0.07–96.8 months). The most common site of distant metastasis was the lung ($n = 16$) followed by bone ($n = 4$). Twenty-one patients (79%) had presented with recurrent AJCC stage IVA or IVB disease.

After multiple testing correction, although there was a trend of lymphovascular invasion being associated with worse distant metastasis rates in the salvage surgery subset ($p = .094$), ultimately, no covariates were found to be significantly associated with distant metastasis for all patients or for those who underwent salvage surgery (Tables 3 and 5).

Toxicity—RT was generally well tolerated. Supplemental Table 1, online only, summarizes grade 3 or higher acute radiation-associated toxicity and Supplemental Table 2, online only, displays the prevalence of acute toxicity. Grade 3 or higher mucositis, dermatitis, and dysphagia were experienced by 38%, 17%, and 12% of patients, respectively. Supplemental Table 3, online only, lists the prevalence of chronic radiation-associated toxicity.

DISCUSSION

Recurrent OCC remains a difficult to treat disease irrespective of therapeutic approach. This study demonstrates that surgery with postoperative RT or RT alone can be used for successful salvage of some patients with recurrent oral cavity squamous cell carcinoma. However, rates of survival and disease control are generally inferior to those seen with patients treated initially with surgery and adjuvant RT,[3,8,11] particularly when compared to contemporary series,[4,12] although with shorter follow-up, Gomez et al[4] and Sher et al[12] reported rates of 2-year OS that are substantially greater (63% to 75%) than this present study (46% to 55%).

The current study reveals several novel and previously unreported prognostic factors in recurrent OCCs. These include the association of PNI and age with OS, tumor thickness, and disease-specific death, and primary T classification with local failure. Although these pathologic associations have been demonstrated in studies of primary OCCs,[3,13–17] no previously published reports have established these findings in recurrent OCCs. Rather, what has been previously reported,[5–7,18,19] as we also find in the present study, is that patients with recurrent disease who undergo salvage surgery or have lower-stage disease have improved outcomes.

Please see Table 7 for a summary of contemporary patient series reporting on treatment of recurrent OCCs.[5–7,18,19] Of the limited studies that report specifically on recurrent OCC, Schwartz et al[19]reported a 4-year survival rate of 25% in a study of 38 patients. Of these patients, 27 underwent surgical salvage alone and achieved an approximately 4-year OS rate of 35%. The authors found that the stage of primary tumor, but not recurrent tumor, was predictive of OS ($p < .005$). Similar to the present study, patients who underwent salvage surgery were found to have significantly improved recurrent survival time ($p < .002$), when compared to salvage by RT and/or chemotherapy alone. This is understandable as patients who were not able to undergo salvage surgery at the time of recurrence likely had unresectable and more advanced disease. Other studies examined recurrent head and neck cancers with OCC as a substantial subset. Wong et al[5] reported a 5-year OS rate of 26% in 102 patients with recurrent head and neck cancer after surgical salvage, of which 32% had OCC and 30% received postoperative RT.

In an RT specific study, Studer et al[7] reported a series of 44 patients with recurrent head and neck cancer treated with salvage IMRT with a 2-year disease-specific survival and local failure rate of 59% and 44%, respectively. Twenty-nine patients (66%) had OCC, with 59% of all study patients undergoing salvage surgery before receiving RT. The authors did not find any significant associated factors, only a trend toward significance for disease-specific survival ($p = .1$) in a “high-risk” cohort that combined patients with residual gross tumor, high-grade, or high tumor stage.

Our study had several limitations, including its retrospective nature and some unrecorded pathological data. However, this study confirms the importance of salvage surgery, if possible, and the necessity of optimal surgical margins to maximize clinical outcomes even when incorporating RT. Furthermore, thicker recurrent tumors and higher recurrent T

classification demonstrated prognostic utility in relation to disease-specific death, whereas older age, higher recurrent T classification, and PNI were independently associated with decreased survival. Patients with these risk factors should be considered for multimodal adjuvant therapies as tolerated. One interesting result was the association of primary T classification with local failure after treatment for the recurrent disease. A possible explanation may be that advanced-T-classification tumors at initiation presentation have a greater burden of microscopic disease beyond the resection edge that increases local failure rates even after treatment for recurrent disease. These aforementioned factors should be examined in future studies of recurrent disease.

In conclusion, in this group of patients with recurrent oral cavity squamous cell carcinoma, RT was well tolerated and salvage surgery improved patient outcomes. Clinical outcomes were equivalent or improved when compared to similar studies (Table 7) of recurrent disease.[5,7,19] Because of the difficulty of treating recurrent OCC, future studies should be directed toward additional risk stratification in traditionally defined low/intermediate risk patients who may benefit from adjuvant RT to optimize outcomes at the initial presentation of OCC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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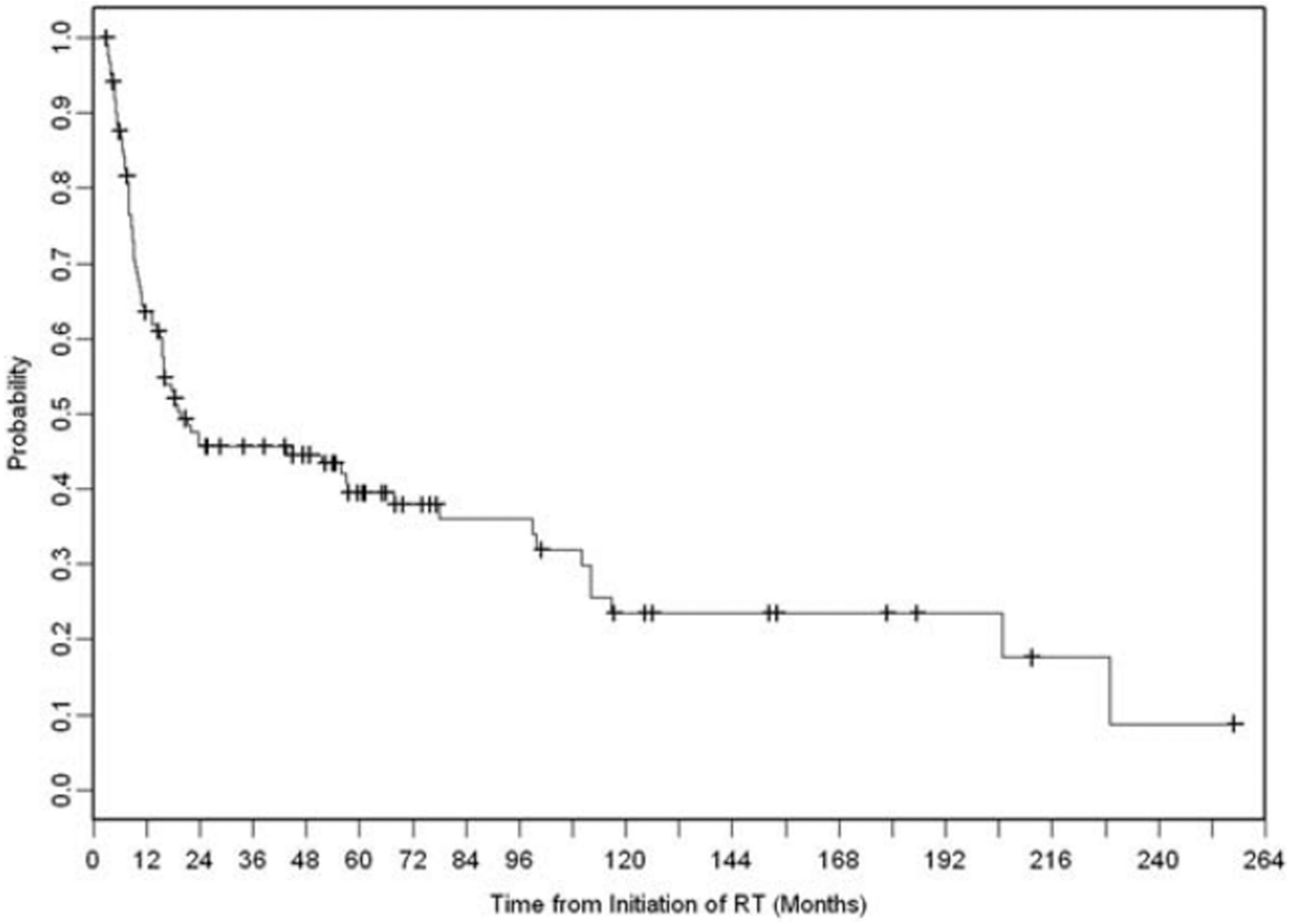

FIGURE 1.
Kaplan–Meier estimate of overall survival for all patients. RT, radiotherapy.

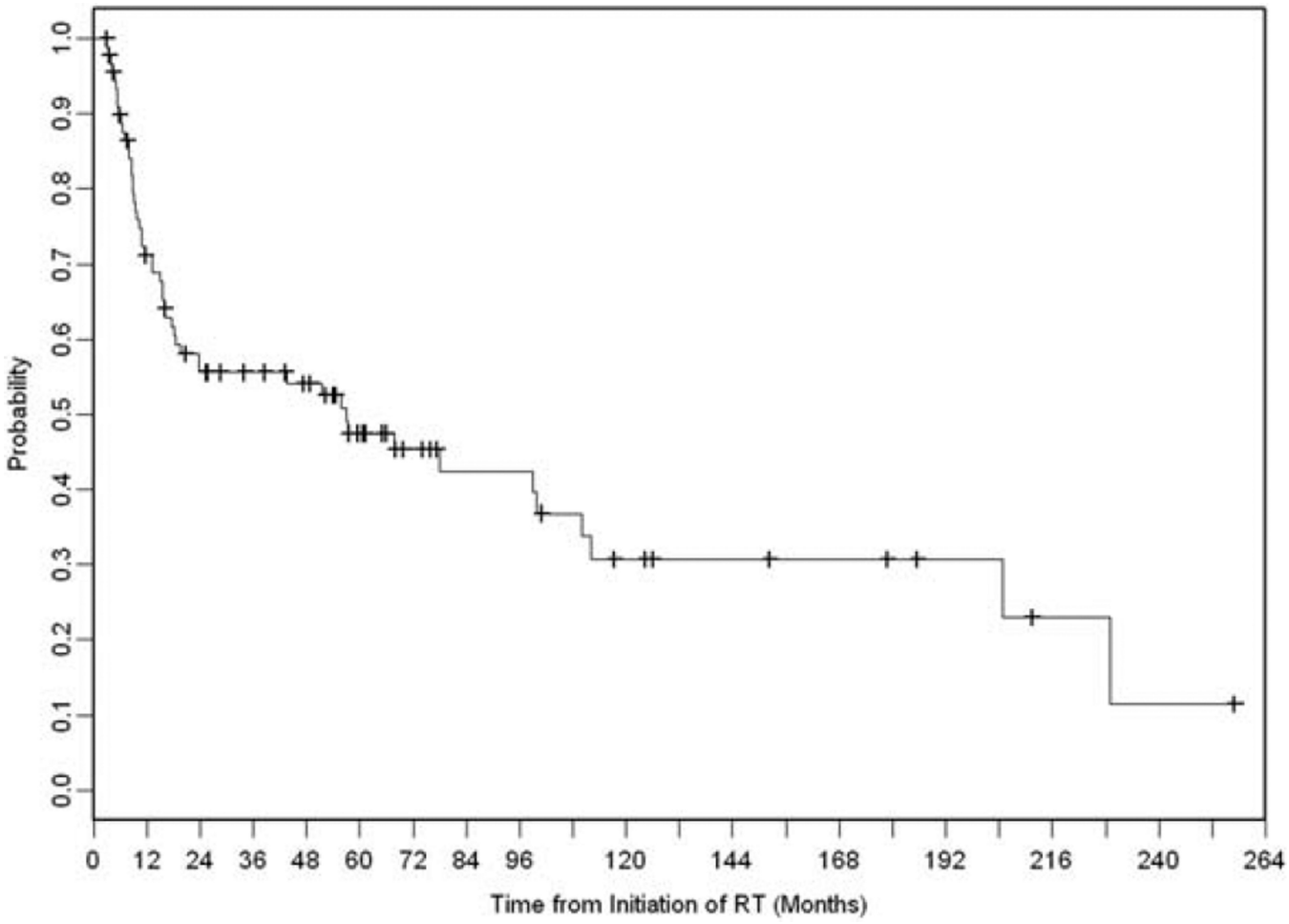

FIGURE 2.

Kaplan–Meier estimate of overall survival for patients who underwent salvage surgery. RT, radiotherapy.

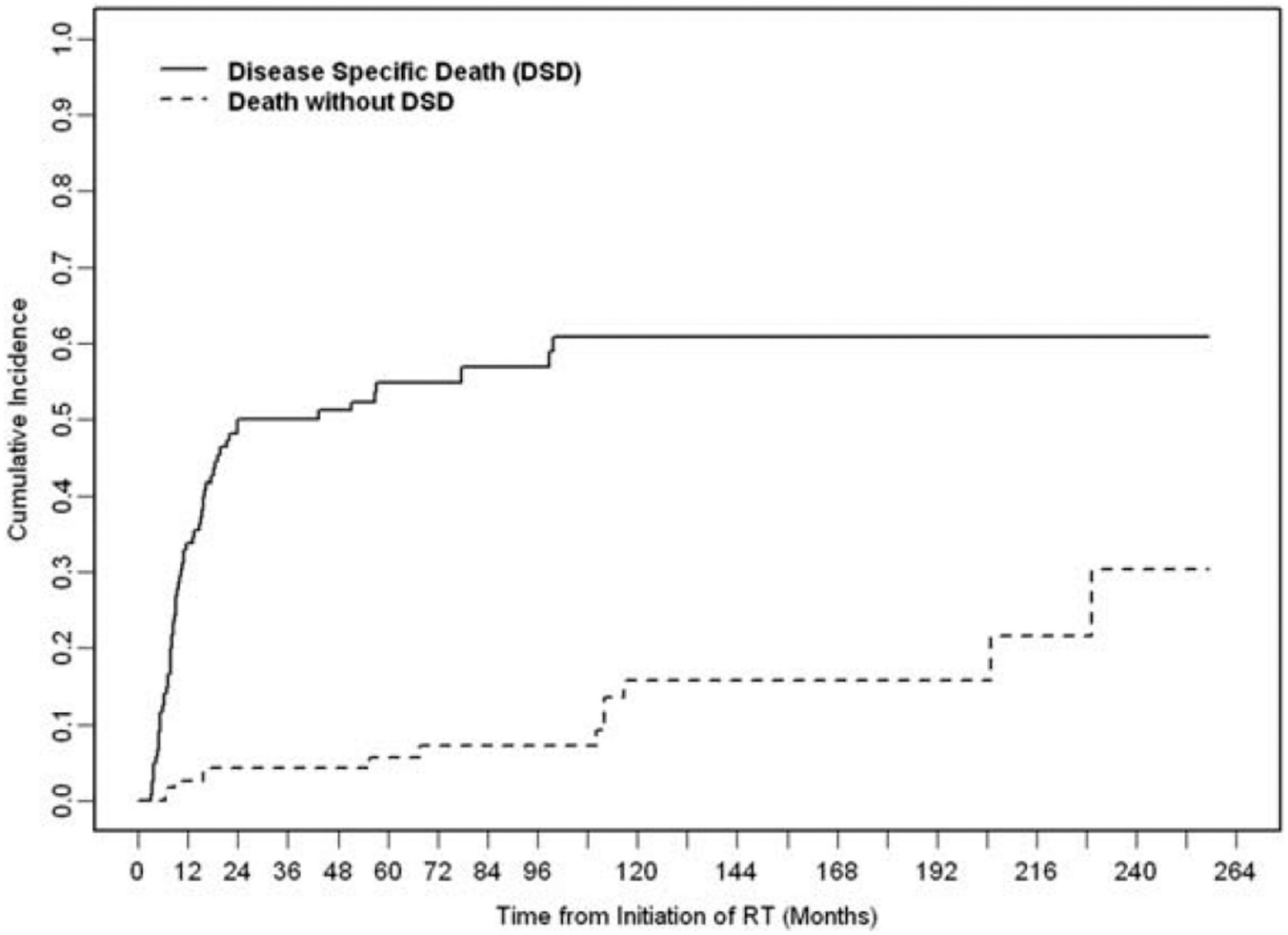

FIGURE 3.
Cumulative incidence of disease-specific death for all patients. RT, radiotherapy.

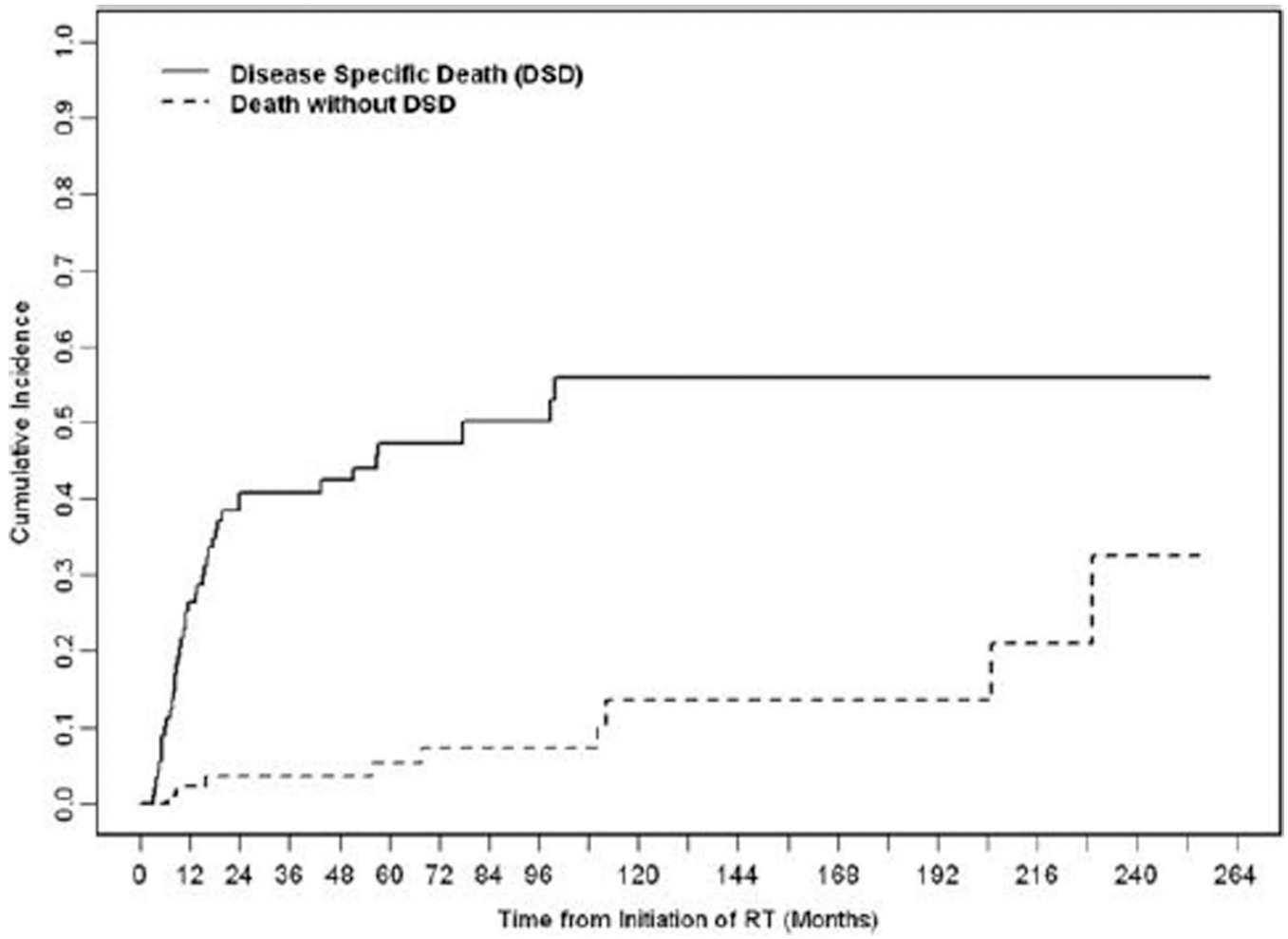

FIGURE 4.

Cumulative incidence of disease-specific death for patients who underwent salvage surgery. RT, radiotherapy.

TABLE 1

Patient characteristics and primary disease subsite.

Characteristic	No. of patients (%)*
Median age (range), y	60 (17–93)
Sex	
Male	77 (62)
Female	46 (37)
Race	
White	101 (82)
Black	8 (7)
Other	14 (11)
Subsite of primary disease	
Oral tongue	65 (53)
Gingiva	18 (15)
Floor of mouth	17 (14)
Buccal mucosa	11 (9)
Lip	6 (5)
Hard palate	4 (3)
Retromolar trigone	2 (2)

*Except as otherwise stated.

TABLE 2

Disease stage and treatment methods.

	Recurrent disease						Primary disease	
	All patients		Postoperative patients		Definitive patients			
T classification	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
T0	45	36	39	43	6	19	0	0
Tis or T1	31	25	27	30	4	13	83	67
T2	24	19	14	15	10	31	29	24
T3	9	7	3	3	6	19	4	3
T4a	8	6	8	9	0	0	2	2
T4b	6	5	0	0	6	19	0	0
Unknown or NR	1	1	0	0	1	3	5	4
N classification								
N0	33	27	19	21	14	44	113	91
N1	26	4	21	23	5	16	4	3
N2	61	50	51	56	10	31	6	5
N3	3	2	0	0	3	9	0	0
Unknown or NR	0	0	0	0	0	0	1	1
AJCC stage *								
0	0	0	0	0	0	0	1	1
I	10	8	7	8	3	9	82	66
II	13	10	7	8	6	19	25	20
III	28	23	21	23	7	22	8†	6
IVA	64	52	55	60	9	28	7†	6
IVB	9	7	1	1	8	25	0	0
Unknown or NR	0	0	0	0	0	0	1	1
Median tumor thickness, cm (range)			0.75 (0.08–6.5)				0.55 (<0.10–2.80)	
Treatment methods								
Surgery								
Yes	91	74	91	100	0	0	123	100

	Recurrent disease						Primary disease	
	All patients		Postoperative patients		Definitive patients			
T classification	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Local resection only	6	5	6	7	N/A		67‡	54
Neck dissection only	39	32	39	43	N/A		0	0
Local resection and ND	46	37	46	51	N/A		56	46
No	32	26	0	0	32	100	0	0
RT								
Conventional RT	68	55	46	51	22	69	0	0
IMRT	55	45	45	49	10	31	0	0
None	0	0	0	0	0	0	123	99
Chemotherapy								
None	68	55	56	62	12	38	124	100
Cisplatin only	34	28	24	26	10	31	0	0
Cetuximab only	12	10	8	8	4	13	0	0
Other or combination	9§	7	3	32	6	19	0	0

Abbreviations: NR, not reported; AJCC, American Joint Committee on Cancer; ND, neck dissection; RT, radiotherapy; IMRT, intensity-modulated radiotherapy; N/A, not applicable.

*For recurrent disease, AJCC stage was for presentation of disease at the time of recurrence (eg, rTNM converted to rI-IV stage).

†Regarding lack of adjuvant therapy for the 15 patients with advanced disease at initial presentation, 7 were advised to undergo observation (of which 3 were node negative and 1 had the radiosensitive genetic disease Fanconi anemia), 3 had intended to undergo RT but the disease recurred before initiation of RT, 2 declined adjuvant therapy, and the remaining 3 had insufficient documentation to determine a specific reason for deferring adjuvant therapy.

‡Includes 1 patient who underwent an unknown surgical operation.

§Five carboplatin-based regimens, 2 cisplatin-based combinations.

TABLE 3

Univariate analysis, impact of prognostic factors on survival and disease control for all patients.

	OS		Disease-specific death		Local failure		Regional failure		Distant metastasis	
Recurrent disease	**Unadj. p value**	**Adj. *p* value***	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**
Age, <65 vs ≥65 y†	.054	.18	.15	.30	.095	.19	.60	.86	.30	0.76
Recurrent T classification, T0–1 vs T2–4	<.0001	**.0005**	.0003	**.003**	.0067	**.045**	.017	.17	.17	0.58
Recurrent N classification, N0 vs ≥N1	.74	.83	.88	.88	.13	.19	.81	.99	.17	0.58
Recurrent AJCC stage I–III vs IV	.089	.22	.26	.37	.033	.11	.051	.20	.013	0.13
Margin status, negative vs positive/close vs no surgery	<.0001	**.0006**	.0011	**.0055**	.0089	**.045**	.97	.99	.60	0.96
Time from diagnosis of primary tumor to start of RT for recurrent disease, ≤12 mo vs >12 mo	.88	.88	.43	.54	.53	.59	.58	.86	.68	0.96
Primary disease Subsite, other vs oral tongue	.20	.27	.24	.37	.80	.80	.99	.99	.99	0.99
Initial T classification, T0–1 vs T2–4	.13	.26	.024	.08	.056	.14	.32	.64	.62	0.96
Initial N classification, N0 vs N1–3	.20	.27	.49	.54	.20	.25	.061	.20	.87	0.96
Initial AJCC stage I vs II–IV	.21	.27	.14	.30	.11	.19	.20	.50	.87	0.96

Abbreviations: OS, overall survival; Unadj., unadjusted *p* value; Adj., adjusted *p* value; AJCC, American Joint Committee on Cancer; RT, radiotherapy.

*Adjusted *p* values of .05 or less are in **bold** font. Multiple testing adjusted *p* value using Benjamini and Hochberg False Discovery Rate controlling procedure (Benjamini Y, Hochburg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. *J R Statist Soc B* 1995;57:289–300).

†In entire column, all left-sided variables had increased survival or lower death/failure rates than right-sided variables for significant factors.

TABLE 4

Multivariate analysis, impact of prognostic factors on survival and disease control for all patients.

		OS		Disease-specific death	
Recurrent disease	**No. of patients**	**HR (95% CI)**	***p* value***	**HR (95% CI)**	***p* value**
Recurrent T classification					
T0–1	77			1.00	
T2–4	47			1.99 (1.16–3.42)	**0.01**
Margin status					
Negative	58	1.00			
Positive/close	28	1.75 (0.95–3.25)	0.07		
No surgery	34	3.70 (2.07–6.60)	<**0.0001**		

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval.

** p* values of .05 or less are in **bold** font. Factors whose univariate adjusted *p* value <.1 were considered candidates for the stepwise multivariate model.

TABLE 5

Univariate analysis, impact of prognostic factors on survival and disease control for the 91 patients who underwent surgery.

	OS		Disease-specific death		Local failure		Regional failure		Distant metastasis	
Recurrent disease	**Unadj. *p* value**	**Adj. *p* value***	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**	**Unadj. *p* value**	**Adj. *p* value**
Age, <65 vs ≥65 y†	.029	.081	.11	.20	.16	.23	.77	.96	.92	.93
Recurrent T classification T0–1 vs T2–4	.0029	**.020**	.013	.091	.011	**.050**	.027	.38	.52	.67
Recurrent N classification N0 vs N1–3	.61	.73	.96	.96	.064	.13	.74	.96	.13	.46
Recurrent AJCC stage I–III vs IV	.076	.18	.15	.23	.045	.11	.12	.41	.044	.31
Margin status, negative vs positive/close	.0070	**.033**	.066	.17	.0070	**.049**	.82	.96	.28	.59
High tumor grade, no vs yes	.60	.73	.92	.96	.50	.58	.11	.41	.42	.66
PNI, no vs yes vs NR‡	.0029	**.020**	.043	.15	.048	.11	.79	.96	.20	.57
Lymphovascular invasion, no vs yes vs NR§	.22	.38	.071	.17	.34	.43	.94	1.00	.0067	.094
ECE, yes vs no vs NR††	.85	.85	.93	.96	.11	.18	.33	.81	.082	.38
Tumor thickness, <0.75 cm vs ≥0.75 cm vs NR¶	.0096	**.034**	.0041	.057	.12	.18	.077	.41	.38	.66
Time from diagnosis of primary tumor to start of RT for recurrent disease, ≤12 mo vs >12 mo	.63	.73	.82	.96	.55	.60	1.00	1.00	.30	.59
Primary disease Subsite, other vs oral tongue	.76	.82	.74	.96	.86	.86	.53	.96	.90	.93
Initial T classification T0–1 vs T2–4	.19	.38	.030	.14	.0059	**.049**	.59	.96	.52	.67
Initial N classification N0 vs N1–3//	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Initial AJCC stage I vs II–IV	.28	.43	.11	.20	.015	.053	.35	.81	.93	.93

Abbreviations: OS, overall survival; Unadj. *p* value, unadjusted *p* value; Adj. *p* value, adjusted *p* value; AJCC, American Joint Committee on Cancer; PNI perineural invasion; NR, not reported; ECE, extracapsular extension; RT, radiotherapy; NA, not applicable.

[*] Adjusted *p* values of .05 or less are in **bold** font. Multiple testing adjusted *p* value using Benjamini and Hochberg False Discovery Rate controlling procedure (Benjamini Y, Hochburg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. *J R Statist Soc B* 1995;57:289–300).

[†] In entire column, all left-sided variables had increased survival or lower death/failure rates than right-sided variables for significant factors.

[‡] Fifty-seven pathologic records identified explicitly reporting presence or absence of PNI.

[§] Sixty-two pathologic records identified explicitly reporting presence or absence of lymphovascular invasion.

[††] Sixty-nine pathologic records identified explicitly reporting presence or absence of ECE.

[¶] Sixty-seven pathologic records identified explicitly reporting recurrent tumor thickness.

[//] Only 4 patients had ≥N1 disease, initial N classification was excluded from analysis.

TABLE 6

Multivariate analysis, impact of prognostic factors on survival and disease control for the 91 patients who underwent surgery.

		OS (51 died, 40 censored)		Disease-specific death (42 disease-specific death, 9 died w/o disease-specific death, 40 censored)		Local failure (27 local failure, 31 died w/o local failure, 33 censored)	
Recurrent disease	**No. of patients**	**HR (95% CI)**	***p* value***	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age, y							
<65	57	1.00					
≥65	34	2.55 (1.38–4.70)	0.003				
Recurrent T classification							
T0–1	66	1.00		1.00			
T2–4	25	2.33 (1.26–4.31)	0.007	1.99 (1.06–3.76)	0.03		
Margin status							
Negative	59					1.00	
Positive/close	28					2.86 (1.25–6.54)	0.01
PNI							
No	32	1.00					
Yes	25	3.96 (1.85–8.51)	0.0004				
NR	34	1.53 (0.76–3.08)	0.23				
Tumor thickness							
<0.75 cm	34			1.00			
≥0.75 cm	32			2.56 (1.12–5.82)	0.03		
NR	25			3.58 (1.54–8.32)	0.003		
Primary disease Initial T classification							
T0–1	66					1.00	
T2–4	22					2.51 (1.11–5.65)	0.03

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; PNI, perineural invasion; NR, not reported.

*Factors whose univariate adjusted *p* value < .1 were considered candidates for the stepwise multivariate model.

TABLE 7

Selected series of patients with recurrent oral cavity cancers.

Series, year	No. of patients	Recurrent stage III–IV	Rate of isolated regional recurrence prior to salvage treatment	Salvage treatment	OS
Schwartz et al[19] (2000)	38	74%	16%	S (71%)	25% (4 y)
				RT + C (29%)	
Wong et al[5] (2003)	106	≥51%*	40%	S ± RT (27%)†	Approx. 26% (5 y)‡
				RT ± C (43%)	
				C (25%)	
				Supp (35%)	
Koo et al[18] (2006)	31§	52%	42%	S ± RT (42%)	Approx. 30% (5 y)
				C ± RT (32%)	
				Supp (26%)	
Studer et al[7] (2008)	29††	95%	32%	S + RT ± C (59%)	≤59% (2 y)¶
				RT ± C (41%)	
Studer et al[6] (2012)	38	NR	29%	S ± RT (74%)	48% (5 y)
				RT ± C (26%)	
Present study	123	81%	36%	S + RT ± C (74%)	40% (5 y)
				RT ± C (26%)	

Abbreviations: OS, overall survival; S, surgery; RT, radiotherapy; C, chemotherapy; Supp, supportive care; Approx. approximately; NR, not reported.

*This value is likely to be greater. Fifty-four of the 106 patients with recurrent oral cavity cancer presented with regional or locoregional recurrence, however, of the 52 locally recurrent only patients, T classification was not reported and presumed to be T2 or less for purposes of this table.

†Breakdown is for treatment of the total 377 patients with recurrent head and neck cancer.

‡Of 102 patients with recurrent head and neck cancer after surgical salvage with or without RT.

§Thirty-one non-distant metastatic patients of 36 patients with total recurrent cancer reported.

††Of 44 patients with total recurrent head and neck cancer.

¶Only disease-specific survival reported, OS was not reported.