

Analysis of Treatment Results for Floor-of-Mouth Cancer

Donald G. Sessions, MD; Gershon J. Spector, MD; Jason Lenox, MS; Sarah Parriott, MPH;
Bruce Haughey, MBChB; Clifford Chao, MD; James Marks, MD; Carlos Perez, MD

Objective: This study reports the results of treating floor-of-mouth cancer with five different treatment modalities with long-term follow-up. **Study Design:** Retrospective study of 280 patients with floor-of-mouth cancer treated in the Department of Otolaryngology—Head and Neck Surgery at Washington University Medical School (St. Louis, MO) from 1960 to 1994. **Methods:** Patients with biopsy-proven squamous cell carcinoma of the floor of mouth who were previously untreated were treated with curative intent by one of five modalities and were all eligible for 5-year follow-up. The treatment modalities included local resection alone, composite resection alone (with neck dissection), radiation therapy alone, local resection with radiation therapy, and composite resection with radiation therapy. Multiple diagnostic, treatment, and follow-up parameters were studied using standard statistical analysis to determine statistical significance. **Results:** The overall 5-year disease-specific survival (DSS) was 56% with death due to tumor in 44% of patients. The 5-year cumulative disease-specific survival (CDSS) was 0.61 (Kaplan-Meier probability) with a mean of 8.3 years and a median of 9.7 years. The DSS by treatment modality included local resection (76%), composite resection (63%), radiation therapy (43%), local resection with radiation therapy (61%), and composite resection with radiation therapy (55%). Overall, there was no significant difference in DSS by treatment modality. Recurrence at the primary site (41%) was the most common site of treatment failure. Nineteen percent of patients had recurrence in the neck. Eighty-eight percent of initial recurrences occurred within 60 months after the onset of treatment. Metastasis to a distant site occurred in 30% of patients. Twenty percent of these patients had second primary cancers, and 53%

of these patients died of their second primary cancers. **Conclusions:** Significantly improved 5-year DSS was seen in the patients with clear margins, early clinical tumor stage, and negative nodes. Significantly decreased 5-year survival was seen in the patients with involved margins, advanced clinical tumor stage, positive nodes, and tumor recurrence. Patients with no clinically positive nodes (cN0) can be observed safely for regional nodal disease and subsequent positive nodes can be treated as they occur with no adverse affect on survival. Because of high recurrence rates at the primary site and neck, and an increased rate of both distant metastasis and the development of second primary cancers, patients should be monitored closely for a minimum of at least 5 years. **Key Words:** Floor-of-mouth cancer, surgery, survival outcome.

Laryngoscope, 110:1764–1772, 2000

INTRODUCTION

This study presents the results of treating floor-of-mouth (FOM) cancer with five different treatment modalities and discusses parameters significant for tumor recurrence and tumor death.

MATERIALS AND METHODS

Retrospective review of patients in the Tumor Registry Project of the Department of Otolaryngology—Head and Neck Surgery of the Washington University Medical School (St. Louis, MO) revealed 869 patients with primary squamous cell carcinoma (SCCA) of the oral cavity. Of these, there were 280 patients with a biopsy-proven SCCA primary arising in the floor of the mouth who were previously untreated, who were treated with curative intent by one of five modalities, and whose treatment date was before January 1, 1995. All patients were eligible for 5-year follow-up. Of the 280 patients, 7 were lost to follow-up and one had an unknown cause of death. These eight patients were considered to have died of cancer. Tumors were staged using the 1997 American Joint Committee on Cancer (AJCC)/UICC criteria.¹ The terms “cT” and “cN” indicate clinical (pretreatment) tumor and node staging, respectively.

The ages of these patients were from 18 to 88 years with 31% less than 56 years, 40% between 56 and 65 years, and 28.9% older than 65 years. Men made up 77% (n = 215) of the patient population. Eighty-eight percent of patients were white (n = 195) and 11% were black. Treatment occurred in the following de-

From the Departments of Otolaryngology—Head and Neck Surgery (D.G.S., G.J.S., B.H.) and Radiation Therapy (C.C., C.P.), Washington University School of Medicine and the Barnes-Jewish Hospital Foundation (J.L., S.P.), St. Louis, Missouri.

Dr. Marks is currently with the Division of Radiation Therapy, Missouri Baptist Hospital, St. Louis, Missouri.

Supported by a grant to the Barnes-Jewish Hospital Foundation by Bob and Karen Isaacs.

Editor's Note: This Manuscript was accepted for publication June 8, 2000.

Send Correspondence to Donald G. Sessions, MD, Campus Box 8115, 660 South Euclid Avenue, St. Louis, MO 63110, U.S.A.

cadets: 1950s, 0.4% (1); 1960s, 19.6% (55); 1970s, 36.8% (103); 1980s, 31.4% (88); and 1990s, 11.8% (33).

The five treatment modalities included local resection (LR), 11.1% (31); composite resection with resection of the primary and neck dissection (CR), 11.4% (32); radiation therapy alone (XRT), 16.1% (45); local resection with radiation therapy (LR/XRT), 10% (28); and composite resection with radiation therapy (CR/XRT), 51.4% (144). After resection of the primary tumor, pathological examination with frozen sections was routinely performed.

If any of the examination results were positive, more tissue was removed until results were frozen-section negative. All patients with node-positive necks were treated with neck dissection, XRT, or a combination of both. Selected patients with N0 necks were observed, and the necks were treated only if subsequent nodal disease appeared. Patients treated with XRT alone were treated with external-beam radiation alone, radiation implant alone, or a combination of external-beam radiation and radiation implant.

Standard analysis methods including the Kaplan-Meier method, the log-rank test, the χ^2 -Fisher's exact test, the Wilcoxon test, and logistic regression were used to determine statistical significance. Events described as significant in the present study indicate that the event achieved statistical significance, *P* value being less than or equal to .05, with its subsequent *P* value listed.

Survival analysis definitions included the following:

1. Five-year observed survival rate (OS): This rate is reported as the percentage of patients alive greater than 5 years divided by the total number of patients and includes all deaths, regardless of cause, reflecting the total mortality in the patient group. This is also known as the absolute survival rate.
2. Five-year disease-specific survival rate (DSS): This rate is reported as the percentage of patients alive greater than 5 years divided by the total number of patients who died of the tumor of interest (tumor death). This rate includes only deaths specifically due to FOM tumor and excludes all non-tumor-related deaths in the patient group. This is an adjusted survival rate (non-tumor-related deaths are censored) and is also known as the determinate survival rate.
3. Cumulative survival rate: This rate describes the probability of surviving the most recent time interval multiplied by the probabilities of surviving all previous intervals. This rate can reflect the probability of death due to all causes—the cumulative observed survival (COS)—or of deaths due to tumor, the cumulative disease-specific survival (CDSS) with non-tumor-related deaths being censored.

Quality of life (QOL) measurements were available for 82 patients (29.3%). Parameters studied included voice quality, respiratory and deglutition status, ability to function in everyday life, employment capability and status, and residual deficits.

RESULTS

Patient Population

Table I indicates the clinical staging for the overall patient population (*n* = 280). Most patients had tumors less than 4 cm in size with T1 (105) and T2 (107) totaling 77% of the population. One hundred sixty-two patients (58%) had no clinically positive lymph nodes at the time of presentation (N0).

Overall Survival

Five-year DSS was 56.4% (128/227) with 43.6% (99/227) of patients dying of disease. The 5-year OS was 45.7%. Figure 1 compares the 5-year CDSS and the COS rates. The CDSS 5-year rate was significantly higher than the COS 5-year rate (*P* = .017). The CDSS, with FOM tumor death as the event of interest, had a mean of 8.3 years and a median of 9.7 years. The median of 9.7 years was the lower confidence interval, because the median had not been reached at the end of study. The cumulative probability of surviving 5 years, and all previous periods, was 0.6174 (non-tumor-related and non-FOM-tumor-related deaths were censored). The COS, with any death as the event of interest, had a mean of 7.0 years and a median of 4.0 years, and the cumulative probability of surviving 5 years, and all previous periods, was 0.4464.

Table II indicates overall 5-year survival by stage grouping. Patients with stage I disease had a statistically significant better DSS 5-year rate than stage III and/or stage IV (*P* = .006). Stage groups I and II combined had a significantly higher 5-year DSS than stages III and IV combined (*P* = .001). Stage I (72.4%) DSS 5-year rate was not significantly different from stage II DSS (62.8%), which was not significantly different from stage III DSS (44.4%), which was not significantly different from stage IV DSS (46.9%). There was not a statistically significant difference in the OS 5-year rate between stage groups.

Table III shows the effect of combining cT and cN on overall survival. Patients with cT1 and cT2 combined had a significantly higher 5-year DSS than those with cT3 and cT4 (χ^2 test, *P* = .001). The 5-year DSS rate of patients with cT1 (67.1%) was not significantly different from that of patients with cT2 (60.2%). The rate for cT2 was significantly higher than that for cT3 (31.4%) (*P* = .004), but cT3 and cT4 (40.9%) rates did not significantly differ.

There was a significant difference in DSS among cT stages, regardless of cN stage (*P* = .002). When cN = 0,

TABLE I.
Clinical Staging for Overall Patient Population (*n* = 280).

cT Stage	cN Stage				cT (n)
	cN0	cN1	cN2	cN3	
cT1	78/27.9%	14/5.0%	14/5.0%	0	106
cT2	62/22.1%	23/8.2%	20/7.1%	2/0.7%	107
cT3	13/4.6%	13/4.6%	14/5.0%	0	40
cT4	9/3.2%	5/1.8%	11/3.9%	2/0.7%	27
cN (n)	162	55	59	4	280

	Disease Specific 5-year Survival Rate	Observed 5-year Survival Rate
Yes	128/56.4%	128/45.7%
No	99/43.6%	152/54.3%
(n)	227	280

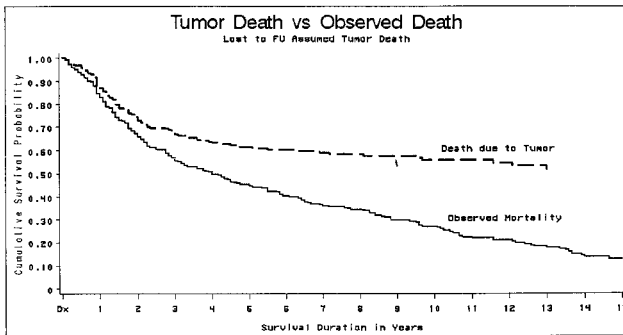


Fig. 1. The cumulative disease-specific survival rate over time (dashed line), and the cumulative observed survival rate over time (solid line). The Kaplan-Meier method was used to generate these survival curves.

there was not a significant difference in 5-year DSS among cT stages. Patients with cT3cN1, cT3cN2, and cT4cN2 staging had significantly lower 5-year survival rates than the rest of the sample population ($P = .039$).

Survival and Treatment Modality

Table IV shows the five treatment modalities by stage group. Local resection (LR) was used for treating earlier lesions, and CR/XRT was used more commonly for treating advanced cancers. Table V shows the DSS 5-year rates for stage by treatment modality. Overall, the 5-year DSS by treatment modality was as follows: LR, 76.2%; CR, 62.5%; XRT, 43.2%; LR/XRT, 60.9%; and CR/XRT, 54.9%. Stage I patients treated with XRT alone and with CR alone had a lower 5-year DSS than patients treated with the other three treatment modalities ($P = .003$).

Tables VI through X show the 5-year DSS for each of the five treatment modalities by cTNM stage. In the patients with cT1N0 there was a significant difference in 5-year DSS related to treatment modality. Patients treated with LR, LR/XRT, and CR/XRT had a higher 5-year DSS than patients treated with XRT alone or CR alone (Fisher's exact test, $P = .003$).

Considering cT only, irrespective of N stage, when cT stage was 1, then XRT alone and CR alone had a significantly lower DSS than the other treatment modalities. Overall, there was no correlation between DSS and treatment modality.

There was no significant difference in DSS between patients treated with external-beam XRT alone, radiation implant alone, and a combination of external-beam XRT and implant. Looking at individual radiation dose or even dose grouping, there was no significant relationship to DSS. The CDSS for 5000 to 5999 cGy was 0.73 with a mean survival of 9.2 years.

Nodal Disease

One hundred sixty-two patients (57.9%) were N0 at the time of presentation. Fifty-five patients (19.6%) were N1, 59 (21.1%) were N2, and 4 (1.4%) were N3. Of all patients with positive nodes, 80.0% had positive ipsilateral nodes and 20.0% had bilateral nodal disease.

Patients with cN0 had a significantly higher 5-year DSS rate than those with cN1 and/or cN2 (Fisher's exact test, $P = .013$). Similarly, patients with cN0 had a significantly better CDSS compared with patients with clinically positive nodes (cN+) (log-rank test, $P = .0048$; Wilcoxon test, $P = .0013$). Among cN+ stages, there was no difference in DSS (cN1, 45.7%; cN2, 42.9%; and cN3, 66.7%).

CDSS at 5 years for cN0 patients was 0.6951 with mean survival of 9.2 years and median survival estimated at 12.08 years. CDSS at 5 years for patients with cN+ was 0.5073 with mean survival of 5.64 years and median survival of 6.33 years.

In regard to cN stage only (irrespective of cT stage), there was a significant difference in survival by treatment modality. When cN = 0, LR alone or combined CR/XRT had statistically higher DSS than the use of CR alone or XRT alone (χ^2 test, $P = .009$). For any patient with positive clinical nodes (cN+), combined CR/XRT had a significantly improved DSS 5-year rate.

There was no significant difference in survival between patients with cN0 whose initial treatment was observation with neck treatment reserved for subsequent neck disease and patients whose necks were treated at the same time as the primary (DSS, $P = .171$; OS, $P = .998$). There was no statistical difference in survival between patients who had either ipsilateral or bilateral disease.

Recurrence

Table XI indicates the site of recurrence after treatment of FOM cancer. Recurrence at the primary site (41.2%) is more than twice as common as recurrence in the neck (18.5%). Metastasis to a distant site occurred in 30.3% of this patient population. The mean and median times to recurrence were 24.5 months and 13 months. Eighty-eight percent of initial recurrences (87/98) occurred within 60 months. There was no significant relationship between the rate of recurrent disease and treatment modality.

Recurrence of tumor statistically affected survival. In the patients with no recurrence the 5-year CDSS probability

TABLE II.
Overall 5-Year Survival by cTNM Stage Grouping.

Stage Grouping	Disease-Specific Survival n = 227		Observed Survival n = 280	
	No.	%	No.	%
I	42*	72.4	42	53.9
II	32	62.8	32	51.6
III	24*	44.4	24	38.7
IV	30*	46.9	30	38.5

* $P = .006$ by χ^2 test.

TABLE III.
Disease-Specific 5-Year Survival for Clinical T and N Stage (n = 227).

cT Stage	cN Stage				cT (n)
	cN0	cN1	cN2	cN3	
cT1	42/72.4%	5/45.5%	8/61.5%	—	106
cT2	32/62.8%	11/55.0%	9/56.3%	1/100%	107
cT3	5/45.5%	4/30.8%*	2/18.2%*	—	40
cT4	5/55.6%	1/50.0%	2/22.2%*	1/100%	27
cN (n)	162	55	59	4	227

* $P = .039$ by χ^2 test.

was 0.7953, but with recurrence it was 0.2963 ($P = .0001$). Salvage of patients with local recurrence resulted in CDSS of 0.4790, which was significantly higher than salvage after neck recurrence (0.2182) or distant metastasis (0.1838) ($P = .0001$). The mean survival (CDSS) of patients with local recurrence was 6.28 years; with neck recurrence, 3.55 years; and with distant disease, 4.14 years. The mean and median times to death after local/neck recurrence were 1.2 years and 0.6 years, respectively. The mean and median times to death for patients with distant metastatic disease were 5.2 months and 3 months, respectively.

Resection Margins

Resection margins were positive in 37.4% (88/235), close in 11.5% (27/235), and clear in 51.1% (120/235) of the patients treated surgically (n = 235). Patients with clear margins had a significantly higher 5-year DSS rate than the patients with close/involved margins ($P = .015$). Patients with clear margins were more likely to be alive, whereas patients with close/involved margins have a higher rate of tumor-related death (χ^2 test, $P = .007$). Patients with close/involved margins had an increased probability of dying of uncontrolled tumor in the primary site, of uncontrolled neck metastases, or of the primary/neck combined site.

Patients with clear margins had a significantly higher cDSS with a mean of 8.7 years and a median of 12.1 years than patients with close/involved margins (log-rank test, $P = .0377$; Wilcoxon test, $P = .0460$). The median of 12.1 years was the lower confidence interval, since the median had not been reached at the end of study. The mean and median cDSS for patients with close/involved

margins were 7.7 years and 11.5 years, respectively. The cumulative probability of surviving 5 years and all previous periods was 0.7148 for patients with clear margins, and it was 0.5536 for patients with close/involved margins (non-tumor-related and non-FOM tumor-related deaths were censored, and patients treated only with XRT were excluded).

Treatment Complications

Surgical complications included infection (5%), wound slough (9.6%), orocutaneous fistula (6.1%), carotid artery exposure/blowout (1.1%), and delayed fatality (1.4%). Fifty-eight percent of these complications were related to the use of combined surgery and XRT. There was a significant increase in the rate of orocutaneous fistula in those patients with combined surgery and radiation treatment (Fisher's exact test, $P = .038$).

Complications after XRT included ulceration of the FOM, necrosis, bone exposure, and orocutaneous fistula. Late radiation complications developed in 41% of patients treated by external-beam irradiation and implant. Most of these complications appeared within 1 year of the implant. Treatment included improved oral hygiene and observation, treatment with hyperbaric oxygen, excision of selected ulcers, local sequestrectomy, and excision of the osteoradionecrotic mandible with reconstruction. There was no significant relationship between complications and radiation dose. Because of these complications, the use of radiation implants was eliminated in the mid 1970s and replaced by external-beam XRT.

TABLE IV.
Five Treatment Modalities and cTNM Stage Grouping.

Stage	Modality					cTNM Stage (n)
	Local	Composite	Radiation	Local and Radiation	Composite and Radiation	
I	26/33.3%	6/7.7%	16/20.5%	11/14.1%	19/24.4%	78
II	3/4.8%	2/3.2%	9/14.5%	14/22.6%	34/54.8%	62
III	2/3.2%	7/11.3%	7/11.3%	1/1.6%	45/72.6%	62
IV	1/1.3%	16/20.5%	13/16.7%	2/2.6%	46/59.0%	78
Treatment (n)	31	32	45	28	144	280

TABLE V.
Disease-Specific 5-Year Survival for Treatment Modality by cTNM Stages (n = 227).

Treatment	All Stages	cTNM Stage I	cTNM Stage II	cTNM Stage III	cTNM Stage IV	Rx (n)
Local resection	16/76.2%	13/81.2%	1/50.0%	2/100%	0/0.0%	21
Composite resection	15/62.5%	1/25.0%*	2/100%	5/100%	7/53.9%	24
Radiotherapy	16/43.2%	5/41.7%*	2/33.3%	2/33.3%*	7/53.9%	37
Local resection and radiotherapy	14/60.9%	6/75.0%	5/41.7%	1/100%	2/100%	23
Composite resection and radiotherapy	67/54.9%	17/94.4%	22/75.9%	14/35.0%*	14/40.0%	122
cTNM (n)	227	58	51	54	64	227
χ^2 /Fisher's exact test	$P = .158$	$P = .0032$	$P = .059$	$P = .0045$	$P = .401$	

*Significant $P < .05$ by χ^2 /Fisher's exact test.

Cause of Death

Table XII indicates the cause of death in this patient population. Cancer-related deaths included those due to uncontrolled primary disease (16.8%), uncontrolled neck disease (6.1%), uncontrolled disease in both the primary site and the neck (2.1%), and distant metastases (9.6%). Ten percent of patients died of a second primary cancer. The most common cause of death in this group was intercurrent disease (36.4%).

Treatment Over the Decades

Treatment modality changed over the decades (1950s–1990s). In the 1960s and 1970s, combined CR/XRT, as well as XRT alone, was more commonly used. In the 1960s and early 1970s, external beam XRT and implant were used for treatment of the primary. From the mid 1970s on, external-beam XRT replaced the use of implants because of the high number of late radiation complications associated with implants. In the 1980s, there was an increase in local resection and CR without XRT and a decrease in XRT alone. In the 1990s there was an increase in the use of CR alone.

In the 1960s and 1970s, tumors were predominately cT1 and cT2 with few cT4 tumors. In the 1980s, the number of patients with cT1, cT2, and cT3 tumors stayed the same and there was a dramatic increase in cT4 tumors. In the 1990s, cT4 became the dominant stage of tumor at presentation (36.4%). There was no statistical difference in either the 5-year DSS or the CDSS over the four decades.

Second Primary Cancer

Fifty-five patients (19.6%) had second primary cancers. Twelve patients had synchronous cancers with their tumors becoming evident either 6 months before, or after, their diagnosis of the FOM cancer with 75% of these tumors in the head and neck. Forty-three patients had metachronous tumors with 28 showing up greater than 6 months before their FOM cancer, and 15 greater than 6 months after. Metachronous tumors tended to arise in the head and neck at about the same rate as in more distant sites. Head and neck sites included pharynx, larynx, oral cavity, and salivary glands. Distant sites included lung, liver, and gastrointestinal tract.

Twenty-nine patients (10.4% of all patients/52.7% of those with a second primary) died of their second primary cancer. There was no significant difference in CDSS for patients whose second primary was in the head and neck area (0.56) compared with patients with second primaries in distant sites (0.58). With a second primary in the head and neck, the mean and median survivals were 6.3 and 7.7 years, respectively, and with one in a distant site they were 6.9 and 8.8 years. There was no difference in CDSS whether the second primary was previous to the FOM cancer (0.56), synchronous with it (0.34), or subsequent to it (0.73).

Parameters Related to Treatment Success or Failure

Success in terms of a significant improvement in DSS included the following: 1) clear margins; 2) stages cT1 and

TABLE VI.
Disease-Specific 5-Year Survival for Clinical T and N Stage (n = 21): Local Resection.

cT Stage	cN Stage			cT (n)
	cN0	cN1	cN2	
cT1	13/81.3%	1/100%	1/100%	18
cT2	1/50.0%	—	—	2
cT3	1/100%	—	—	1
cT4	—	—	—	—
cN (n)	19	1	1	21

$P = .338$ by χ^2 test.

TABLE VII.
Disease-Specific 5-Year Survival for Clinical T and N Stage (n = 24): Composite Resection.

cT Stage	cN Stage			cT (n)
	cN0	cN1	cN2	
cT1	1/25.0%	2/100%	1/33.3%	9
cT2	2/100%	2/100%	2/100%	6
cT3	1/100%	—	1/100%	2
cT4	2/40.0%	—	1/50.0%	7
cN (n)	12	4	8	24

$P = .445$ by χ^2 test.

TABLE VIII.
Disease-Specific 5-Year Survival for Clinical T and N Stage
(n = 37): Radiation.

cT Stage	cN Stage			cT (n)
	cN0	cN1	cN2	
cT1	5/41.7%	0/0%	2/50.0%	17
cT2	2/33.3%	2/100%	2/66.7%	11
cT3	0/0%	1/50.0%	0/0%	6
cT4	1/100%	—	1/50.0%	3
cN (n)	21	5	11	37

$P = .697$ by χ^2 test.

cT2 better than cT3 or cT4 (or both); 3) stages cT1N0 and cT2N0 better than all other cTN stages; 4) clinical stage I in relation to stages III or IV; and 5) stage cN0 better than cN1 and cN2. Failure in terms of a significant decrease in DSS included the following: 1) involved margins; 2) stages cT3N1 and cT3N2 and cT4N2 have lower survival rates than the other cTN stages; and 3) for cN0, XRT alone has lower survival rates than other treatment modalities.

Parameters significantly useful in predicting death due to tumor included recurrence, involved margins, and cT staging. The only parameter that was a statistically significant predictor of recurrence was clinically positive lymph nodes (cN+). A patient with recurrence is 16.1 times (odds ratio) more likely to have a tumor-related death than one without a recurrence. A patient with involved margins is 2.6 times (odds ratio) more likely to have a tumor-related death than one with clear margins. A patient with cT4 is 8.4 times (odds ratio) more likely to have a tumor-related death than a patient with a cT1 tumor.

Nodal disease was associated with a decrease in 5-year DSS when positive in the submandibular level (χ^2 , $P = .001$) or in the anterior cervical lymphatic chain level (χ^2 , $P = .011$). Bone involvement did not predict a significant increase in tumor death, nor did invasion of soft tissue, vessels, or nerves.

Quality of Life

Quality of life information was available for 82 patients. Treatment modalities represented included LR (13), CR (19), XRT (1), LR/XRT (6), and CR/XRT (43).

TABLE IX.
Disease-Specific 5-Year Survival for Clinical T and N Stage
(n = 23): Local Resection With Radiation.

cT Stage	cN Stage			cT (n)
	cN0	cN1	cN2	
cT1	6/75.0%	—	1/100%	9
cT2	5/41.7%	1/100%	—	13
cT3	—	—	—	—
cT4	1/100%	—	—	1
cN (n)	21	1	1	23

$P = .348$ by χ^2 test.

Seventy-seven patients (94%) were functional in their daily lives. Swallowing was normal and asymptomatic in 90% of patients treated with LR (n = 19) but only in 57% of the patients who had CR (n = 62). Six patients (7%) required a permanent gastrostomy tube for feeding, and four patients (5%) required indwelling tracheotomy tubes. Composite resection had a significant impact on patients' ability to return to work after treatment for FOM cancer. After treatment with LR, 74% of patients were capable of working compared with 23% of patients treated with CR (Fisher's exact test, $P = .00025$). Vital statistics for this patient population are presented in Table XIII.

DISCUSSION

Survival

Overall 5-year DSS has been reported as between 60%^{2,3} and 65%.⁴ Shaha et al.⁴ reported overall determinate 5-year cure rate of 65% of 320 patients. Stages I through III had better determinate survival than stage IV (88%, 80%, and 66% vs. 32%). Hicks et al.⁵ confirmed this reporting on 99 patients. Stages I through III (95%, 86%, and 82%) 5-year DSS was significantly better than stage IV (52%). Pernot et al.⁶ and Shons et al.⁷ reported that DSS was related to tumor size (T stage). Shons et al.⁷ reported that survival was also related to the number of positive lymph nodes and systemic metastasis. In the current study, overall DSS by stage included stage I at 72%, stage II at 63%, stage III at 44%, and stage IV at 47%. Survival was related to cT and cN and positive margins.

TABLE X.
Disease-Specific 5-Year Survival for Clinical T and N Stage (n = 122): Composite Resection
With Radiation.

cT Stage	cN Stage				cT (n)
	cN0	cN1	cN2	cN3	
cT1	17/94.4%*	2/28.6%	4/100%	—	29
cT2	22/75.9%*	6/40.0%	4/45.5%	1/100%	56
cT3	3/42.9%	3/27.3%	1/12.5%	—	26
cT4	1/50.0%	1/50.0%	0.0%	1/50.0%	11
cN (n)	56	35	28	3	122

$P = .001$ by χ^2 test.

Lymph Nodes

The treatment of the N0 neck continues to be challenging. Some authors have maintained that all patients should have the N0 neck treated either surgically with neck dissection or with XRT. Our data indicate that N0 patients can be observed and followed closely with the neck treated for subsequent neck disease with no adverse effect on survival. This course of action should be recommended only in those patients who can be followed closely with frequent examinations and computed tomography (CT) scanning.

Recurrence

Shons et al.⁷ reported a series of 94 patients with recurrence significantly related to stage (stages I, 9%; II, 17%; III, 32%; and IV, 52%). Hicks et al.⁵ noted correlation of recurrence with margin status. Fu et al.² noted recurrence rate of 91% within 2 years of primary treatment. Marks et al.⁸ reported 80% failure above the clavicle in 18 months. Shons et al.⁷ noted that 78% of recurrence occurred in 36 months. Reported salvage rates after recurrence included Shons et al.,⁷ 28% alive at 1 year; Zelefsky et al.,⁹ 50% (4/8); Pernot et al.,⁶ 16% (9/55); Fu et al.,² 61% (14/23); and Delclos and Linberg,¹⁰ 38% (3/8). In the current study, recurrence occurred most commonly in the primary site. One-half of patients had a form of local recurrence (Table X). The only significant predictor of recurrence was clinically positive nodes. Recurrent tumor significantly decreased survival.

Margins

Loree and Strong¹¹ reported 31% positive margins (43/137). Positive margins were correlated with T stage, increased local recurrence, and decreased 5-year survival. They noted that treating patients with positive margins with postoperative XRT did not improve survival. This was in contrast to Zelefsky et al.,⁹ who reported positive margins in 23% of patients and that this did not affect survival. They noted that giving greater than 6000 cGy produced improved survival.

In the current study, there were positive margins in 38.5% of patients. Patients with involved margins had a significantly increased probability of dying of uncontrolled tumor at the primary site or at the combined primary and neck site. It is thought that the high number of patients with positive margins is due to clinical underestimation of

TABLE XI.
Site of Recurrence.

Site of Recurrence	n	%
Local	49	41.2
Neck	22	18.5
Distant	36	30.3
Local and neck	8	6.7
Local and distant	2	1.7
Local, neck, and distant	1	0.8
Other	1	0.8
Total	119	

TABLE XII.
Causes of Death.

	n	%
Alive	47	16.8
Uncontrolled primary	47	16.8
Uncontrolled neck	17	6.1
Uncontrolled metastasis	27	9.6
Uncontrolled primary and neck	6	2.1
Complications of treatment	5	1.8
Second primary cancer	28	10.0
Intercurrent disease	102	36.4
Unknown	1	0.4
Total	280	

the primary tumor. These tumors are often infiltrative and diffuse with indistinct edges. Despite the routine use of frozen-section examination of margins at the time of what was thought to be an aggressive resection, subsequent permanent sections often showed close or positive margins.

In this study there was no statistically significant survival difference between patients who had positive margins in their resection specimen who were treated with postoperative XRT and those who had no postoperative irradiation, irrespective of the dose used. This indicates the need for more extensive resections initially with frozen sections for margins at the time of initial resection and the need to repeat resection in areas where positive margins show up on the permanent specimen.

Complications

Surgical complications. Shaha et al.⁴ reported an overall complication rate of 20% with 2.5% (8/320) opera-

TABLE XIII.
Vital Statistics (N = 280)

Vital Statistic	#	%
Alive, no evidence of disease	37	13.2
Alive, salvaged no evidence of disease	5	1.8
Alive, cancer status unknown	1	0.3
Alive with cancer, primary recurrence	0	—
Alive with cancer, distant recurrence	1	0.3
Alive with second primary cancer	2	0.7
Subtotal	46	16.4
Dead, no evidence of disease	85	30.3
Dead, salvaged no evidence of disease	13	4.6
Dead, with cancer, persistent disease	25	8.9
Dead, with cancer, recurrent disease	75	26.8
Dead, with cancer, second primary	36	12.8
Dead, with cancer, other	2	7
Dead, cancer status unknown	5	1.8
Subtotal	234	83.6
Total	280	—

tive deaths. The complications included orocutaneous fistula, hematoma, wound infection, and systemic infections. Surgical complications in the current study included wound infections (5%), wound slough (10%), and orocutaneous fistula (6%). These complications were commonly related to the combination of surgery and irradiation.

Radiation therapy. Fu et al.² reported 10% bone exposure or necrosis (16/153), 3% soft tissue necrosis (5/153), and 6% orocutaneous fistula (10/153). Of the fistula group, 9 of 10 patients had previous XRT. Aygun et al.¹² reported 17% bone and soft tissue necrosis with symptoms occurring between 4 and 53 months after treatment with a mean period of 16 months.

Gilbert et al.¹³ reported 22% of patients with osteoradionecrosis between 3 months and 6 years with half of the events within the first year. Delclos and Linberg¹⁰ reported 22% (8/37) soft tissue necrosis and osteoradionecrosis. In the present study 41% of patients treated with a combination of external-beam XRT and implant developed late radiation complications. Because of these findings, the use of implants was eliminated in the mid 1970s.

Distant Metastasis

Fu et al.² reported distant metastases in 9% of patients (14/153). In the present report metastasis to a distant site occurred in 30% of patients. The mean time to death in these patients was 5.2 months.

Second Primary

Fu et al.² reported that second primary cancers developed in 36% of patients (55/153). Twelve patients had more than two primaries. Mortality in the patients with second primaries was 54% (30/55).

Aygun et al.,¹² Guillaumondegui et al.,¹⁴ and Marks et al.⁸ reported second primary rates of 23% (21/93), 24% (25/104), and 25% (32/126), respectively. The present study reports a second primary rate of 20% with a mean survival of 6.6 years. We would recommend the use of chemoprevention measures in this patient population to decrease the rate of second primary cancers.

Summary

Floor-of-mouth cancer is a lethal disease that spreads to regional lymph nodes early. Seventy-seven percent (213 of 280) of this study population consisted of patients with cT1 (n = 106) and cT2 (n = 107) disease, of which 34% (n = 73) were node positive. The 5-year DSS for the overall patient population was 56% with death due to tumor in 44%. The 5-year CDSS was 0.61 with a mean of 8.3 years and a median of 9.7 years.

The 5-year DSS by treatment modality included the following: LR, 76%; CR, 63%; XRT, 43%; LR/XRT, 61%; and CR/XRT, 55%. Overall, there was no significant difference in DSS by treatment modality.

Fifty-eight percent of patients were cN0 at presentation. These patients had a significantly better DSS, cumulative and 5-year, than patients with clinically positive lymph nodes. There was no significant difference in DSS between patients with cN0 whose initial treatment was observation of the neck with neck treatment reserved for

subsequent neck disease and those patients whose necks were treated at the same time as the primary ($P = .17$).

Recurrence at the primary site (primary only, 41%; all primary failures, 50%) was more than twice as common as recurrence in the neck (neck only, 19%; all neck failures, 26%). Eighty-eight percent of initial recurrences occurred within 60 months. Metastatic disease to a distant site occurred in 30% of patients. Twenty percent of these patients had second primary cancers, and 53% (29/55) of these patients died of their second primary cancer.

Of patients who had surgery, 37.4% had positive resection margins. Patients with clear margins had significantly better DSS than patients with involved or close margins.

CONCLUSION

In regard to treatment of FOM cancer, none of the five modalities had a significant survival advantage. Significant improvement in 5-year DSS was seen in the patients with clear margins, early cT stage, and negative nodes. Significant decrease in 5-year DSS was seen in the patients with involved margins, advanced cT stage, positive cN, and tumor recurrence. Patients with no clinically positive neck nodes (cN0) can be observed safely for regional nodal disease and subsequent positive neck nodes can be treated as they occur with no adverse effect on survival.

All efforts should be made to obtain clear and wide resection margins including the use of multiple frozen sections at the time of the original surgical procedure. If there are subsequent close or positive margins on permanent sections, then repeat resection of that area is recommended to obtain negative margins. Treating patients with close or positive margins with postoperative XRT alone has not significantly improved survival.

Because of high recurrence rates at the primary and neck sites and the high rates of both distant metastatic disease and the development of second primary cancers, patients should be monitored closely for a minimum of at least 5 years.

BIBLIOGRAPHY

1. American Joint Committee on Cancer. *Cancer Staging Manual*. edn 5. Philadelphia: Lippincott-Raven, 1997:24-30.
2. Fu KK, Lichter A, Galante M. Carcinoma of the floor of mouth: an analysis of treatment results and the sites and causes of failures. *Int J Radiat Oncol Biol Phys* 1976; 1(9-10):829-837.
3. Million RR, Cassisi NJ. Oral cavity. In: Million RR, Cassisi NJ, eds. *Management of Head Neck Cancer: A Multidisciplinary Approach*. Philadelphia: JB Lippincott, 1984: 239-237.
4. Shaha AR, Spiro RH, Shah JP, Strong EW. Squamous carcinoma of the floor of the mouth. *Am J Surg* 1994;148(4): 455-459.
5. Hicks WL, Loree TR, Garcia RI, et al. Squamous cell carcinoma of the floor of mouth: a 20-year review. *Head Neck* 1997;19(5):400-405.
6. Pernot M, Hoffstetter S, Peiffert D, et al. Epidermoid carcinomas of the floor of mouth treated by exclusive irradiation: statistical study of a series of 207 cases. *Radiother Oncol* 1995;35(3):177-185.
7. Shons AR, Magallanes F, McQuarrie D. The results of aggressive regional operation in the treatment of cancer of the floor of the mouth. *Surgery* 1984;96(1):29-34.

8. Marks JE, Lee F, Smith PG, Ogura JH. Floor of mouth cancer: patient selection and treatment results. *Laryngoscope* 1983;93:475–480.
9. Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. *Int J Radiat Oncol Biol Phys* 1993;25(1):17–21.
10. Delclos L, Linberg RD. Squamous cell carcinoma of the oral tongue and floor of mouth. Evaluation of interstitial radium therapy. *Am J Roentg* 1976;126(2):223–8.
11. Loree TR, Strong EW. Significance of positive margins in oral cavity squamous carcinoma. *Am J Surg* 1990;160(4):410–4.
12. Aygun C, Salazar OM, Sewchand W, Amornmarn R, Prempre T. Carcinoma of the floor of the mouth: a 20-year experience. *Int J Radiat Oncol Biol Phys* 1984;10(5):619–626.
13. Gilbert EH, Goffinet DR, Bagshaw MA. Carcinoma of the oral tongue and floor of mouth: fifteen years' experience with linear acceleration therapy. *Cancer* 1975;35(6):1517–1524.
14. Guillaumondegui OM, Oliver B, Hayden R. Cancer of the anterior floor of the mouth: selective choice of treatment and analysis of failures. *Am J Surg* 1980;140(4):560–562.