Original Article

The efficacy of postoperative radiation therapy in patients with carcinoma of the buccal mucosa and lower alveolus with positive surgical margins

Badakh Dinesh K, Grover Amit H

Dr. D. K. Gosavi Memorial, Siddhivinayak Ganpati Cancer Hospital, Miraj-Sangli Road, Miraj, India

Correspondence to: Dr. Dinesh K. Badakh, E-mail: dineshbadakh@yahoo.co.in

Abstract

PURPOSE: A retrospective analysis to determine the efficacy of postoperative radiation therapy, in patients of carcinoma of the buccal mucosa and lower alveolus with pathologically verified positive surgical margins (PSM). **MATERIALS AND METHODS:** Ninety-four patients were analysed, who underwent surgery plus postoperative radiation therapy. Twenty-nine patients (31%) had PSM. Other pathological factors like nodal stage, number of nodes, bone involvement etc. were also analysed. **RESULTS:** Disease free survival (DFS) of patients with a PSM was significantly worse when compared with those with negative surgical margins (NSM). Poor DFS was also observed for variables like nodal stage, number of nodes and extranodal extension and radiation dose. In multivariate analysis only two variables showed significant impact on DFS, those were surgical margins and number of nodes. **CONCLUSION:** To conclude in our study median dose of 60 Gy in PSM patients was not able to improve DFS and showed poor results as compared with NSM patients. There is also evidence from other studies, to suggest that post-operative radiation doses upto 60 Gy may not be sufficient to overcome this poor prognostic factor. To overcome this poor prognostic group patients, we in our institution are now employing radiation dose intensification and altered fractionation in an effort to imrove our results. In physically fit patients we are trying to administer concomitant chemotherapy along with radiation treatment.

Key Words: Buccal mucosa, Positive surgical margins, Radiation

Introduction

Due to various anatomic factors and because most of oral cavity cancer patients present at an advanced stage, adequate margins for clearance are not achieved in around twenty to thirty percent of these patients. Some studies have not been able to demonstrate a clear benefit with radiation in patients with positive margins,[1,2] while others have shown that with doses more than or equal to 60 Gy, excellent local control can be achieved with both surgical margin positive and negative patients.[3] The purpose of the present study was to analyse the outcome of postoperative radiation in patients with positive surgical margins (PSM). Along with PSM other poor prognostic factors like nodal stage, number of nodes, bone involvement, skin involvement etc were also analyzed.

Materials and Methods

Patients with stage III and IV buccal mucosa and lower alveolus cancers, treated with postoperative radiation in the department of radiation oncology, were analysed in this study. Site wise analysis and follow up analysis are shown in Table 1.

Patients selected for a retrospective analysis in this study

Table 1: Disease site and follow up analysis

Site	Total
Lower Alveolus	20
Buccal Mucosa	74
Follow UP Analysis	
Lost for follow up	1
Disease free survival	41
Local Failure	30
Distant Failure	4
Died	18

were from a period of January 1998 to December 2000. Patients in this study had been adviced postoperative radiation depending only on their pathological staging, Stage III or IV patients either due to their Tumor stage or nodal stage or due to both were selected for analysis and only one patient was of stage T2N0M0 but given postoperative radiation and selected for analysis because he was having PSM. Pathological tumor stage and nodal stage are shown in Table 2. Overall analysis of data is shown in Table 3.

Criteria for inclusion in this study were the following:

All patients should have histological proven squamous cell carcinoma of buccal mucosa or lower alveolus; the specimens were reported or reviewed by the hospital panel of pathologists.
No prior radiotherapy to the primary site or neck.
No clinically palpable, residual or recurrent disease at the primary or nodal site, at the initiation of radiation therapy.
All patients received their radiation therapy in this institute only.
Patients with pathologic stage III and IV and those with PSM irrespective of stage were selected for analysis.
PSM patients were taken as those, with either invasive or in situ carcinoma at surgical margins. Near or close surgical margins are taken as NSM.
Patients should have received, a minimum 44 Gy of postoperative radiation dose.
Those patients who were irregular in radiation schedule were not included in study.

Table 2: Tumor and nodal groups

	T1	T2	T3	T4
Total	0	3	6	85
N 0	0	1	3	39
N 1	0	0	0	14
N 2a	0	1	0	3
N 2b	0	1	3	29

Table 3: Overall analysis

		Total No.	DFS	Failed
Age	25-35 yrs	11	4	7
	35-60 yrs	71	34	37
	>60 yrs	12	8	4
Bone	No involved	43	18	25
	Involved	51	28	23
SM	Negative	65	37	28
	Positive	29	8	21
Nodal	Stage N 0	43	26	17
	Stage N 1	14	11	3
	Stage N 2	37	9	28
Extranodal	Extension -	65	37	28
	Extension +	29	9	20
No. Nodes	0 node	43	26	17
	1 node	18	12	6
	2 nodes	14	5	9
	3 nodes	10	3	7
	4 nodes	9	0	9
RT Dose	56Gy or less	63	36	27
	>56 Gy	31	10	21

SM: surgical margin, No. Nodes: number of nodes, RT dose: radiation dose

A total of ninety-four patients were suitable for the study. Median follow up available was 27 months with range from 0 to 52 months. Patients were pathologically staged according to the American Joint Cancer Committee (AJCC) 1997, staging system. In general, all patients with Clinically palpable lymph nodes and those patients in whom clinical and/or radiological stage was T4, were treated with radical or modified radical neck dissection with preservation of spinal accessory nerve and/or internal jugular vein and/ or sternocleidomastoid muscle when ever possible. Those with clinically negative nodes underwent supraomohyoid neck dissection(lymphnode Levels I, II, and III were removed).

Radiation treatment was delivered via cobalt 60 employing two parallel opposing lateral portals to encompass the primary site and whole neck. After 46 Gy the entire spinal cord was taken out of treatment portal. Patients were generally treated with 200 cgy daily fractions. The dose of radiation given was 44 Gy - 64 Gy with a median dose of 56 Gy for all patients. In our institution we were treating a PSM patients with a radiation doses of 60 Gy or more. Surgical margins were only criteria used to give different radiation doses depending upon a PSM or NSM. The median dose in PSM patients was 60 Gy (range 48 to 64 Gy), as compared to those with NSM patients receiving a median of 55 Gy (range 44 to 60 Gy).

Survival and time to failure was calculated from starting of radiation. SPSS-10 Soft ware was used for statistical analysis. Comparison between groups was performed using a bivariate analysis Spearman's correlation, significance (2-tailed) at 0.05 level (at 95% confidence interval) and Kaplan-Meier survival curves were plotted and compared with log rank test and results of this test given below each curve. Multivariate analysis was done using Cox Regression analysis, backward Wald analysis including factors only which had statistically significant difference with bivariate analysis spearman's correlation and long rank test. Disease free survival (DFS) was defined as patients who are remaining free of disease at the primary site, regional nodal site and free of distant metastases for more than 24 months. Patients who failed locoregionally or distally before 24 months were taken as failed and analysed accordingly. One patient was lost to follow up and taken as failed.

Results

In retrospective analysis of these 94 patients with a median age of 50 years (range 28-75), and a male to female ratio of 5.2:1, (Males: 79 and Females: 15), showed a DFS of 48.9% (46 patients disease free at 24 months).

(1) PSM and DFS pattern

It was found that PSM is a very poor prognostic feature and compromises DFS. Their was a significant difference statistically between the 29 patients (30.9%) with a PSM disease and the 65 patients (69%) with a NSM in terms of DFS (*P* value is 0.0046). This difference was found though a higher dose of radiation was given to PSM patients as compared to NSM patients (Figure 1).

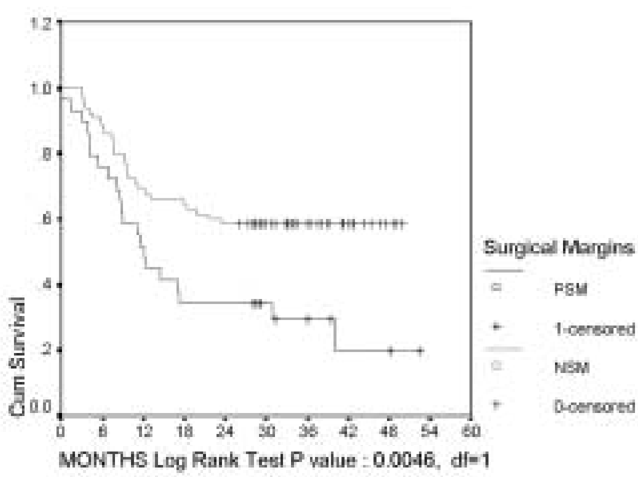

Figure 1: Correlation of positive surgical margin and disease free survival

(2) Analysis of nodal stage and extra nodal extension

It was seen that their was a statistically significant difference between node negative and node positive patients (*P* value 0.0001) and in patients with or without extranodal extension (*P* value 0.0062) with respect to DFS (Figure 2 and 3). Their was no statistically significant difference between No and N1 groups though survival curves showing better survival for N1 group.

(3) Analysis as per number of nodes

Similarly when number of nodes was taken into account, it was seen to correlate inversely with disease free survival i.e. with additional positive nodes the survival went down. With four or more nodes positive disease free survival was very poor. Statistically significant difference in terms of DFS was found (Value 0.0002) (Figure 4).

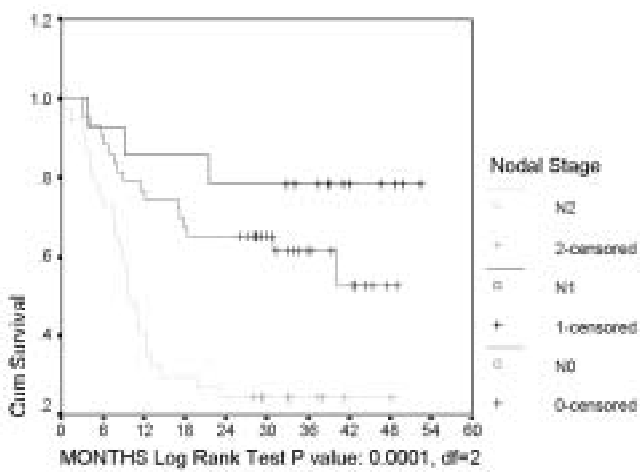

Figure 2: Correlation of nodal stage and disease free survival

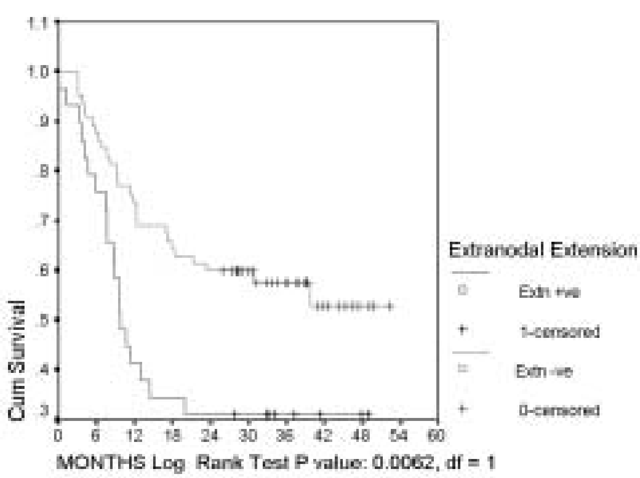

Figure 3: Correlation of extranodal extension and disease free survival

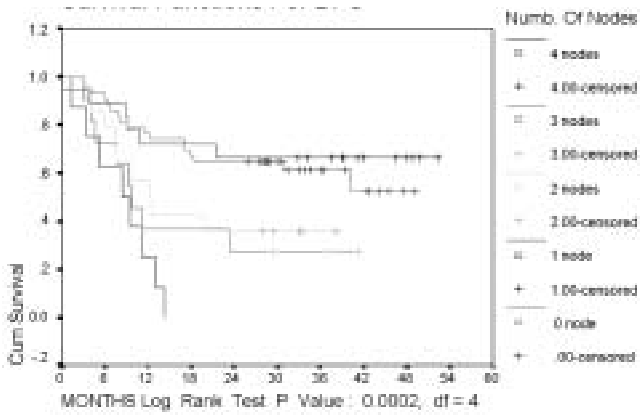

Figure 4: Correlation of number of nodes and disease free survival

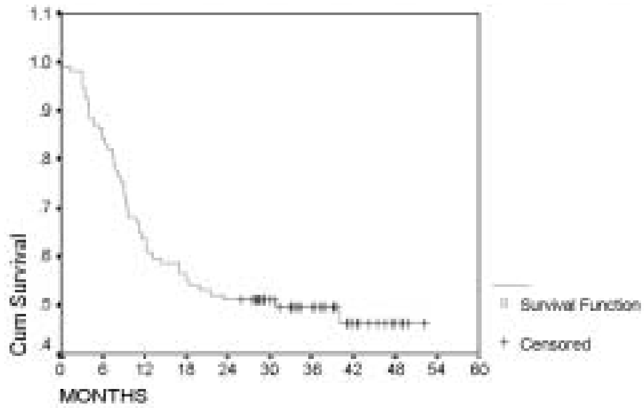

Figure 6: Survival analysis (DFS) for months

(4) Analysis as per radiation dose and DFS

A dose of 56 Gy was taken for dividing patients into two groups, as this was a median dose of radiation received by patients. Group 1 included patients who received a dose equal to or below 56 Gy and patients in group 2 received a dose more than 56 Gy. A significant difference was found in the two groups with respect to DFS and patient group receiving more than 56 Gy of radiation had poor DFS (*P* value 0.0386). This is shown in Figure 5. We think this is because most PSM patients received higher doses in our study.

(5) Other factors

Overall analysis of factors is given in detail in Table 1. Analysis as per age, sex and histopathological grade, bone and skin involvement with respect to DFS and failure pattern was done. Overall DFS is shown in Figure 6.

(6) Multivariate analysis was done by Cox Regression analysis, Backward Wald analysis including factors only which had statistically significant difference with bivariate analysis spearman's correlation and long rank test these variables were Nodal stage, Radiation dose, Number of nodes, Extranodal extension,and Surgical margins. In multivariate analysis only two variables were statistically significant and those were, number of nodes with *P* value 0.000 and surgical margins with *P* value 0.007. Which is shown in Table 4.

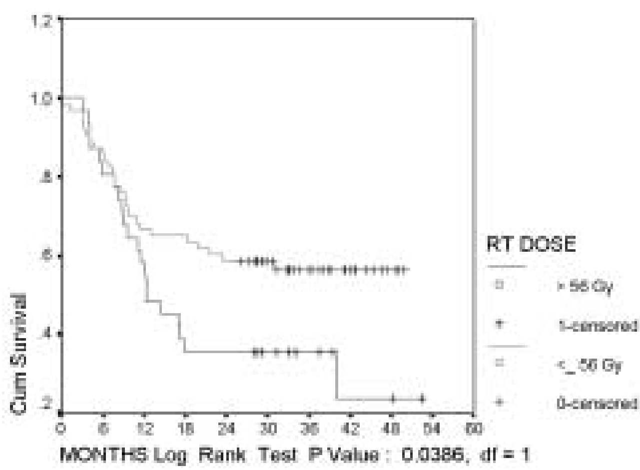

Figure 5: Correlation of dose of radiation therapy and disease free survival

Discussion

In the ninety-four patients analysed, twenty-nine patients had PSM pathologically and that amounts to thirty one percent. The study demonstrates inferior results, even with a higher dose of postoperative radiation in this subgroup of PSM patients as compared with NSM patients. There was a statistical difference in respect to the DFS. Only two factors which turned out to be significant in multivariate analysis were number of nodes pathologically involved and PSM.

As shown in results N1 group had better survival than N0 group, but their was no statistically significant difference between No and N1 groups though survival

Table 4: Cox regression analysis, backward wald type

		SE	Wald	Df	Sig
Step 1	PSM	0.416	3.777	1	0.052
	Extn	0.398	0.363	1	0.547
	No. nodes	0.218	3.366	1	0.067
	Rt dose	0.408	0.010	1	0.920
	Nodal st	0.373	0.022	1	0.883
Step 2	PSM	0.297	7.216	1	0.007
	No. nodes	0.101	17.180	1	0.000

Extn: Extranodal extension, No. nodes: Number of Nodes, Rt dose: Radiation dose; Nodal St: Nodal Stage; Likelihood ratio 377.042, Chi square test 27.973, Degree of Freedom: 5; Only PSM and Number of nodes variable significant in multivariate analysis curves showing better survival for N1 group. Patients in N1 group only 14 patients, less number, and their might not be a much difference in survival patterns in N0 and N1 disease in stage T3 and T4 i.e. advanced T stage.

This study deals with limited subsite of patients, that is only buccal mucosa and lower alveolus patients are studied. Most other studies have included many subsites of head and neck cancers in their study and so more biological variability as per site.[3] In our study all patients received radiation at same center and so ensures more uniformity in radiation treatment.

Literature on PSM was reviewed. Findings of Byers,[1] about prognostic and therapeutic value of frozen section in surgical treatment of squamous carcinoma of head and neck cancers revealed that patients treated with surgery alone with positive surgical margins and inability to achieve negative margins showed a local failure of 80% and the survival at 2 years in these patients with oral cavity cancers was only 10% (PSM was defined as those margins that showed invasive microscopic cancer or carcinoma in situ). In those where the margins were revised and found negative, local recurrence rate was 13% and 2 year survival was 86%. This was equivalent to those who had margins free at the outset. Only one of the twenty patients with margin positive on frozen section survived two years. These patients did not receive postoperative radiotherapy.

In this study of Byers et al,[1] patient group in which it was not possible to attain NSM had poor local control rates and survival, as compared to those with NSM.This patients were treated with surgery alone, they never received postoperative radiation.

Results of Loree,[2] has shown that the percentage of patients with positive margins increases with T stage, in his series 32% of patients had positive margins, but majority were with close margins. In this study PSM was classified as positive according to four criteria: (1) close margin (tumor with in 0.5 cm), (2) Premalignant change in the margin, (3) in situ carcinoma in the margin, (4) invasive microscopic carcinoma in the margin. They also noted that the risk of local recurrence was two times higher in patients with positive margins and 5 year survival was significantly poorer for PSM patients. It was noted that postoperative radiation was ineffective in patients with positive margins. A similar incidence was also noted by Zelefsky,[3] of around 25% in patients of head and neck cancers who underwent surgery.

Other studies have also noted a much higher rate of local relapse and an extremely poor five year survival rate in PSM patients.[4-6] Suen,[7] noted that with PSM, a radiation dose of 60 Gy also was not enough to control disease. Zieske[6] has also observed post-operative radiation to be less effective in these patients.

In our institute patients with PSM are taken as a poor prognostic factor and have thus been treated with a higher dose of radiation. The DFS in PSM patients was 28% (8/29 patients DFS at 24 months).

This result and some of the above studies show that radiation is not that effective in controlling PSM patients as compared with NSM patients Zelefsky,[3] in his analysis of oral cavity cancers and oropharyngeal cancers (excluding oral tongue) with PSM disease who had received radiation dose more than 60 Gy , noted a better local control and 7 year survival than those who had received a radiation dose of less than 60 Gy and difference was statistically significant. This study showed that with doses more than or equal to 60 Gy when used post operatively, for PSM patients, gives a local control rate equivalent to NSM patients.

This clearly shows that there is need to rethink about treating PSM patients more aggressively. Nair[8] has shown that buccal mucosa cancers can be cured with radiation alone. Nair used different schedules of radiation, 45 patients were treated with radical implant(dose 65 Gy in 6 days), Rest nonimplantable patients were treated with radiation dose of 50- 52.5 Gy in 15 fractions over 19 days or 60 Gy in 25 fractions over 33 days. Those failed locoregionally were offered salvage surgery if operable. They reported DFS in fourtytwo percent of patients at 3 years of radiotherapy. So there is no doubt that radiation helps in local control and improving survival.

In some of the above studies no post-operative radiation has been given or else a dose of 45 to 50 Gy has been given to control sub clinical disease. Fletcher,[9] in his textbook, Textbook of radiation therapy, also recommended dose up to 45 to 50 Gy for sub clinical disease and said that it controls sub clinical disease in ninety percent of patients. In sub clinical disease the load of tumor cells as quoted in textbook by Perez,[10] will be above 10[5] cells and cut margin positive patients considering micro extensions this load may be anywhere above 10[5] cells somewhere between 10[6] cells to 10[9] cells. So cut margin positive patients have got a variable tumor load and this load can be much more higher than sub clinical disease. Second post operatively there will be an alteration in the tumor and normal tissue environment, with their blood supply and oxygenation.

Tubiana, Dutreix,[11] in textbook, Introduction to

Radiobiology noted that larger tumors are more difficult to cure compared to small ones. Higher doses of radiation are required to cure large tumors. They mention that clinically non-palpable tumor of diameter between 0 to 5 millimeter may have tumor cell burden as high as 10[8] cells. They also said that for sub clinical disease doses up to 50 Gy are enough because of two reasons;
(1) Tumors with dimensions less than 1 mm^3 are well oxygenated (2) There radio sensitivity is greater because of absence of quiescent cells.

PSM tumor will not be always of dimensions less than 1 mm^3 and thus a tumor bigger than this may have quiescent or radioresistant cells and also hypoxic tumor cells. The authors have suggested the need for larger doses of radiation if there are large number of occult metastases.

In recent article by cooper,[12] about post-operative concurrent radiotherapy and chemotherapy for high risk squamous cell carcinoma of head and neck showed that concomitant chemotherapy and radiation arm had better DFS than radiation alone arm. A total of 70% treatment failures were associated with radiotherapy and 60% with combined therapy. Author concluded with remarks that there data, in combination of with the EORTC data, establish a new standard of care of physically fit patients with high risk head and neck cancer. Author also cautioned not to use such aggressive treatment protocols in physically unfit patients because of their morbidity and mortality.

In our study patient group with PSM had poor DFS as compared with NSM inspite of receiving a median dose of 60 Gy radiation, postoperatively. So it is clear that PSM is independent poor prognostic factor and different strategies need to be employed to bring down its incidence and treat it more radically without increasing morbidity.

Institutional policy

At our cancer hospital the poor prognostic group patients including PSM patients, N2 or more disease and those with extra nodal extension are now treated with radical doses above 64 Gy or more. Along with dose escalation altered fractionation is also being studied in a prospective but nonrandomized trial. We are giving higher doses to both primary and nodal site. In our institution we are also trying to concomitantly administer chemotherapy along with radiation, in view of recent literature in selected group of physically fit patients. Frozen section is being used to bring down the incidence of positive surgical margins.

Conclusion

To conclude in our study median dose of 60 Gy in PSM patients was not able to improve DFS and showed poor results as compared with NSM patients. This study and available published data confirm that patients with PSM have a poor prognosis than those where a complete surgical clearance is possible. This is partly explained by a higher tumor burden and post-operative alteration of the tumor and normal tissue environment. There is also evidence to suggest that post-operative radiation doses upto 60 Gy may not be sufficient to overcome this poor prognostic factor. We in our institution are now employing radiation dose intensification and altered fractionation in an effort to improve our results. In physically fit patients we are trying to administer concomitant chemotherapy along with radiation treatment.

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