

Treatment outcomes of squamous cell carcinoma of the lip: A retrospective study

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Abstract. Oral and lip cancer is the most common type of cancer among males in India. Early stage tumours of the lip (stages I and II) are treated with single modality treatment, using either radiotherapy [external beam radiotherapy (EBRT) or brachytherapy] or surgery. Locally advanced tumours (stages III and IVa) are treated with surgery followed by adjuvant treatment. The aim of the present study was to retrospectively evaluate the clinical profile and treatment outcomes of patients with squamous cell carcinoma of the lip who were treated with radical intent at the Regional Cancer Centre (Thiruvananthapuram, India). For this purpose, a total of 120 patients treated with radical radiotherapy (brachytherapy or EBRT) or surgery with or without adjuvant treatment between January 2010 and December 2016 were eligible for the analysis. Kaplan-Meier analysis was used to generate the survival outcomes. Univariate and multivariate analyses were performed to determine the impact of various patient- and tumour-related factors and treatment modality on outcomes. At a median follow-up time of 67.6 months, the disease-free survival (DFS) and overall survival (OS) rates at 4 years for the entire cohort were 69.1 and 86.7%, respectively. The 4-year OS rates for patients with stage I, II, III and IV disease were 88.9, 95.2, 86.8 and 75.3%, respectively, and the DFS rates were 83.6, 69.5, 78.8 and 42.9%, respectively. Primary tumour (P=0.025), nodal (P=0.005) and composite clinical (P=0.006) stage were found to be significant factors affecting DFS rates in the univariate analysis. However, only the nodal stage (P=0.005) was found to be a significant factor affecting DFS rates in the multivariate analysis. On the whole, the present study demonstrates that the outcomes of patients with

lip carcinoma are favourable when treated at the early stages, and the results from this series are in line with those already published.

Introduction

Oral cancer is a major public health concern in India (1). According to the GLOBOCAN 2020 data, oral and lip cancer accounts for ~177,757 related deaths and 377,713 new cases annually worldwide (2), and for 75,290 related deaths and 135,929 new cases yearly in India. Lip and oral cancer is the most common malignant neoplasm among males in India (3). The age-standardised incidence of oral cancer in Trivandrum (also known as Thiruvananthapuram; India) constitutes 14.5/100,000 males and 5.6/100,000 females (4). At the Regional Cancer Centre in Trivandrum, lip and oral cancer constitutes 21.7% of registered male patients with cancer and 6.8% of female patients (5). Squamous cell carcinoma (SCC) is the most common histological type, which develops from the stratified squamous epithelium of the mucosa. Males are found to be more commonly affected by SCC than females (6). Tobacco, alcohol consumption and the habit of chewing betel nut leaves rolled with lime and tobacco (termed pan), are the common aetiological causes for oral cancer in India. Other factors include exposure to ultraviolet light, human papillomavirus infection, orodental factors, dietary deficiencies, syphilis and chronic candidiasis (6). HPV testing (P-16 immunohistochemistry) is not routinely recommended for oral and lip tumours as the prevalence of HPV in these sites is said to be low, unlike for oropharyngeal malignancies where the HPV incidence is reported to be high.

The American Joint Committee on Cancer Staging Manual (AJCC) is commonly used to stage oral cancer (7). Early stage lip tumours (AJCC stages I and II) are treated with single modality treatment, either using radiotherapy [external beam radiotherapy (EBRT) or brachytherapy] or surgery. The cure and local control rates are high, irrespective of treatment with radiotherapy or surgery for early stage lip carcinoma (8). Locally advanced tumours (AJCC stages III and IVa) are treated with surgery followed by adjuvant treatment (9). The advantage of radiation is an improvement in organ preservation with a positive cosmetic outcome; thus, radiotherapy is often used as the single modality treatment. When using

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brachytherapy, it is possible to deliver a high localised dose of radiation to the tumour with rapid dose fall-off when compared to EBRT (10). To date, to the best of our knowledge, no randomised studies comparing these different treatment strategies have been reported. In the clinic, the type of treatment modality is selected based on the size and location of the tumour, the expected functional outcome and the accessibility of the treatment type (11). The aims of the present study were to retrospectively evaluate the clinical profile and treatment outcomes of patients with SCC of the lip treated with radical intent at the Regional Cancer Centre.

Patients and methods

Patients and data collection. The present study retrospectively analysed the data of all patients with biopsy-confirmed carcinoma of the lip treated with radical radiotherapy (brachytherapy or EBRT) or surgery with or without adjuvant treatment at the Regional Cancer Centre. Only patients who were treated with palliative intent were excluded from the study. A total of 120 patients treated between January 2010 and December 2016 were eligible for the analysis. The case records of each of these patients were reviewed and data on patient demographics, clinical treatment and follow-up details were captured in a structured proforma. The 7th edition of the American Joint Committee on Cancer Staging Manual was used to stage the patients included in the study (12). The follow-up information was collected until November 20, 2021, and if information was not available, the patients were contacted over the telephone and their status was updated accordingly.

Statistical analysis. Survival estimates were generated using Kaplan-Meier analysis using IBM SPSS for windows version 21.0 (13). Disease-free survival (DFS) was defined as the period from the date of diagnosis to the date of first documentation of any recurrence. Overall survival (OS) was defined as the period from the date of diagnosis until death due to any cause, or the date of the last follow-up. Data of all 120 patients were used for the final analysis. Univariate and multivariate Cox regression analyses were performed to determine the impact of the patient- and tumour-related factors and treatment modality on patient outcomes (DFS and OS). Age, sex, performance status, smoking, alcohol consumption, pan chewing, primary tumour stage, nodal stage and composite stage were tested for statistical significance in the univariate and multivariate analyses using the Cox-proportional hazards regression model. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

All 120 patients with SCC of the lip treated with radical radiotherapy (brachytherapy or EBRT) or surgery with or without adjuvant treatment between January 2010 and December 2016 were eligible for analysis. The mean age of the patients included in the study was 62 years (range, 39-89 years). The majority of patients (81.6%) were >50 years of age, and males comprised 52.5% of the study population. The stage-wise distribution of patients was as follows: Stage I, 38 (31.7%); stage II, 26 (21.7%); stage III, 26 (21.7%); and stage IVa, 30

Table I. Baseline characteristics of the 120 patients included in the analysis.

Baseline characteristics	Patients, n (%)
Age, years	
≤50	22 (18.3)
>50	98 (81.7)
Sex	
Male	63 (52.5)
Female	57 (47.5)
Habits-Alcohol use	
Yes	32 (26.7)
No	88 (73.3)
Habits-Smoking	
Yes	28 (23.3)
No	92 (76.7)
Habits-Pan chewing	
Yes	93 (77.5)
No	27 (22.5)
Tumour stage ^a	
I	46 (38.3)
II	45 (37.5)
III	7 (5.8)
IVa	22 (18.3)
Nodal stage ^a	
0	68 (56.7)
I	38 (31.7)
II	14 (11.7)
Composite stage ^a	
I	38 (31.7)
II	26 (21.7)
III	26 (21.7)
IVa	30 (25.0)
Performance status ^b	
0	2 (1.7)
I	104 (86.7)
II	14 (11.7)
Treatment modality	
Brachytherapy	16 (13.3)
Surgery with/without adjuvant treatment	38 (31.7)
Radical external beam radiotherapy	66 (55.0)

^aUsing the American Joint Committee on Cancer Staging Manual (12);

^busing the ECOG scale (28).

(25.0%). The baseline characteristics of these 120 patients are presented in Table I.

Of the 120 patients, 16 patients (13.3%) were treated with brachytherapy, 38 (31.7%) with surgery with or without adjuvant treatment and 66 (55.0%) with EBRT. Of the 16 patients treated with brachytherapy, 15 patients (93.8%) were treated with a dose schedule of 48 Gy in 12 fractions over a period of 6 days and 1 patient (6.7%) was treated using a schedule of

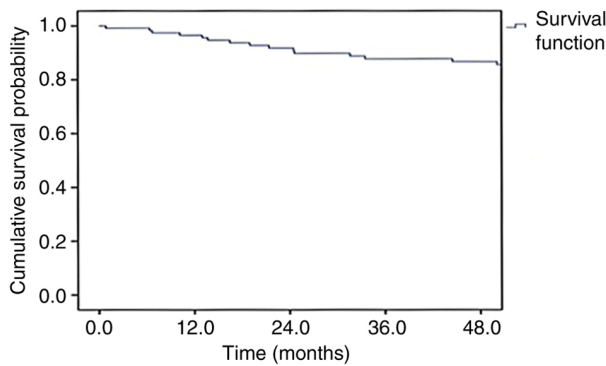


Figure 1. Plot showing the 4-year overall survival time of the cohort.

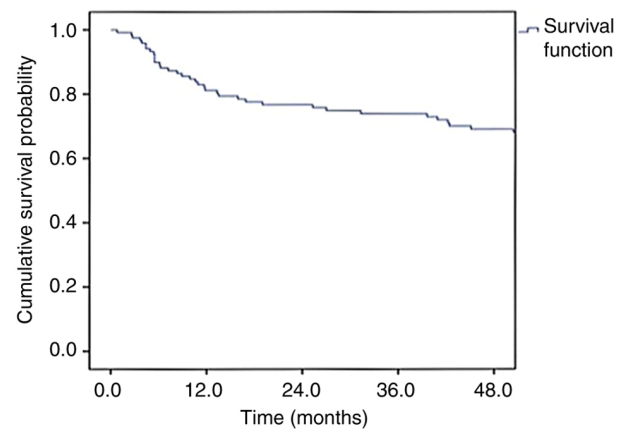


Figure 2. Plot showing the 4-year disease-free survival time of the cohort.

44 Gy in 11 fractions over a period of 6 days. Of the 16 patients treated with brachytherapy, 2 patients (12.5%) had residual disease at the first follow-up and the remaining 14 patients (87.5%) went into clinical remission after treatment. The most commonly used dose schedule for patients treated with EBRT was 52.50 Gy in 15 fractions over 3 weeks in the majority of patients (75.8%) followed by 60 Gy in 26 fractions over 5 weeks (13.6%). At the Regional Cancer Centre, accelerated radiotherapy treatment for oral cancer has been practiced as per the Manchester schedule (52.50 Gy in 15 fractions over 3 weeks) for several decades since 1980 (14). In total, 5 of the 66 patients (7.6%) treated with EBRT received induction chemotherapy and 1 patient (1.5%) received concurrent chemotherapy (3 weekly cisplatin administrations; two cycles) along with radical radiation. The chemotherapy schedules used as induction therapy were single-agent methotrexate (3 patients) and cisplatin + 5-fluorouracil (2 patients). Of the 66 patients treated with EBRT, 11 patients (16.7%) had residual disease at the first follow-up.

Of the 38 patients who were treated with surgery, 20 patients (52.6%) underwent wide local excision of the primary tumour alone, 15 (39.5%) underwent wide excision of the primary tumour with ipsilateral neck dissection and 3 (7.9%) underwent wide excision of the primary tumour with bilateral neck dissection. Bilateral neck dissection was performed in patients with bilateral enlarged cervical nodes. Out of these 38 patients, 4 patients (10.5%) with stage III and IVa disease received induction chemotherapy to decrease the tumour bulk prior to surgery (2 patients received induction chemotherapy with cisplatin + 5-fluorouracil and 2 patients received induction chemotherapy with single-agent methotrexate). A total of 12 patients (31.6%) received adjuvant radiation following primary surgery. Of these 12 patients, 4 patients (33.3%) had node-positive disease, 2 (16.7%) had T3 and T4 disease and 2 (16.7%) exhibited perineural spread in the pathological analysis following surgery. The remaining 4 patients (33.3%) had received induction chemotherapy for stage III and IVa disease prior to surgery. All 12 patients completed the planned standard course of adjuvant radiation using 60 Gy in 30 fractions over 6 weeks. Only 1 of the 12 patients (8.3%) received adjuvant concurrent chemo-radiation with 3 weekly cisplatin (2 cycles), as the patient had extracapsular spread in the nodes.

The median follow-up period was 67.6 months (range, 3.5-128.5 months). The follow-up information available to

calculate 5-year survival figures was limited; therefore, 4-year survival estimates were calculated. With 76% of the follow-up information available at the time of the analysis, the OS and DFS rates at 4 years for the entire cohort were 86.7 and 69.1%, respectively (Figs. 1 and 2). The 4-year OS rates of patients with stage I, II, III and IVa disease were 88.9, 95.2, 86.8 and 75.3%, respectively, and the DFS rates were 83.6, 69.5, 78.8 and 42.9%, respectively (Table II).

Out of the 120 patients treated, 36 patients (30.0%) developed a relapse, and the most common site of failure was at the primary tumour site [in 33 of the 36 (91.7%) patients]. The median time until relapse was 15.9 months (range, 1-113 months). A total of 2 patients (5.6%) developed an isolated nodal relapse and 1 patient (2.8%) developed distant metastasis to the bone.

The 4-year OS rates of patients treated with surgery, EBRT and brachytherapy were 85.6, 85.4 and 92.9%, respectively, and the 4-year DFS rates of patients treated with surgery, EBRT and brachytherapy were 75.4, 65.8 and 68.2%, respectively. Of the 16 patients treated with brachytherapy, 2 patients (12.5%) who had residual disease at the first follow-up later developed progression of the residual disease and another 3 patients (18.8%) developed disease recurrence during follow-up. All of these 5 patients had disease at the primary site. In total, 3 of the 5 patients (60.0%) with disease were later treated with salvage surgery. There were no nodal relapses reported among the patients treated with brachytherapy.

Of the 66 patients treated with radical EBRT, 11 patients (16.7%) who had residual disease at the first follow-up later developed progression of the residual disease and another 13 patients (19.7%) developed disease recurrence during their follow-up period. All of the aforementioned 24 patients had disease at the primary site. Out of the 24 patients with disease, only 6 patients (25.0%) underwent salvage surgery later. There were no nodal relapses reported among the patients treated with radical EBRT.

Of the 38 patients treated with surgery with or without adjuvant therapy, 7 patients (18.4%) developed a relapse. The most common site of relapse following surgery with or without adjuvant therapy was at the primary site [in 4 of the 7 (57.1%) patients]. In addition, 2 patients (5.3%) developed an isolated nodal relapse and 1 patient (2.6%) developed distant

Table II. Overall survival and disease-free survival rates based on the clinical staging and treatment modality of 120 patients.

Parameter	Patients, n	4-year overall survival, %	4-year disease-free survival, %
Clinical stage ^a			
I	38	88.9	83.6
II	26	95.2	69.5
III	26	86.8	78.8
Iva	30	75.3	42.9
Treatment modality			
Brachytherapy	16	92.9	68.2
Surgery with/without adjuvant treatment	38	85.6	75.4
Radical external beam radiotherapy	66	85.4	65.8

^aUsing the American Joint Committee on Cancer Staging Manual (12).

metastasis to the bone. All 3 patients who developed isolated nodal relapse and bone metastasis had stage IVa disease at presentation.

A total of 22 (18.3%) patients developed a secondary malignancy during their follow-up period. The most common site for the development of a secondary malignancy was another subsite in the oral cavity [in 17 of the 22 (77.3%) patients].

The treatment modality used and the patient- and tumour-related factors with potential prognostic value with regard to OS and DFS were recorded and analysed. Primary tumour ($P=0.025$), nodal ($P=0.005$) and composite clinical ($P=0.006$) stage were found to significantly affect DFS rates in the univariate analysis (Tables SI and SII). In the multivariate analysis, only nodal stage ($P=0.005$; Table SIII) was found to be a significant factor affecting DFS rates. The modality of treatment used was not found to be a determinant of DFS or OS.

Discussion

Lip cancer is the most common malignancy arising in the head and neck region, and the majority of cases present at an early stage (8). Early stage lip SCC is associated with high cure rates compared with other head and neck tumours (15). Carcinomas of the lip can be successfully treated by surgery, EBRT or brachytherapy alone or in combination. Different combinations of the aforementioned modalities are used, depending on the stage of the disease and the histopathological findings. The selection of treatment modality is based on various factors that include the resectability of the tumour, disease control probability, the expected functional and cosmetic outcomes, the patient's preference and general condition, and the availability of resources and expertise (9).

When using brachytherapy, it is possible to deliver a high localised dose of radiation to the tumour with rapid dose fall-off, without the need for additional planning margins to be taken into account. This conformity cannot be achieved with any EBRT technique. A study has reported that brachytherapy, when used alone, is an appropriate treatment option for patients with early stage lip tumours (stages T1 and T2-N0) with similar survival and local control rates as surgery (16).

The cosmetic and functional outcomes reported are good with brachytherapy, with no severe complications reported thus far (17).

EBRT and surgical treatment with wide local excision of the primary lesion and negative margins appear to be equally effective in the treatment of early stage lip cancer (8). The histopathological assessment of the primary tumour that can predict the biological behaviour of the tumour and, thereby influence prognosis, is possible following surgical treatment (18). In addition, a surgical procedure may cause a functional and/or cosmetic deficit due to the need to obtain wide margins. By contrast, radiotherapy has been considered to offer better cosmetic and functional results compared with surgery (19). A final histological report is also lacking in patients who receive radiotherapy. Retrospective series [e.g., Ashley *et al* (20)] have reported no differences in local failure and survival rates between surgery and EBRT. To the best of our knowledge, no randomised studies comparing these different treatment strategies have been reported to date. The present study was performed to analyse the clinical profile and treatment outcomes of patients with SCC of the lip treated with radical radiotherapy (brachytherapy or EBRT) or surgery with or without adjuvant treatment at the Regional Cancer Centre.

With a median follow-up period of 67.6 months, the DFS and OS rates at 4 years for the entire cohort of 120 patients were 69.1 and 86.7%, respectively. These survival results are similar to those of previous studies published in the literature (21,22). The 4-year OS rates of patients with stage I, II, III and IVa disease were 88.9, 95.2, 86.8 and 75.3%, respectively, and the DFS rates were 83.6, 69.5, 78.8 and 42.9%, respectively. These results suggest that the cure rate for lip cancer is high, especially when treated at the early stages.

The 4-year OS rates of patients treated with surgery, EBRT and brachytherapy were 85.6, 85.4 and 92.9%, respectively, and the 4-year DFS rates of the patients treated with surgery, EBRT and brachytherapy were 75.4, 65.8 and 68.2%, respectively. These results suggest that the cure rates of patients with early stages of carcinoma of the lip are favourable, whether they were treated with EBRT, brachytherapy or surgery. The 5-year survival rate of patients with lip cancer treated with high dose-rate brachytherapy using moulds was 68.8% in the

study by Unetsubo *et al* (23). This survival value is comparable to those of the present study.

In the present study, 30% of patients developed recurrence following treatment and the majority had local recurrence only. In the literature, the recurrence rates following treatment range from 15 to 30% (21), and the most common sites of recurrence reported are local recurrences (24), similar to those observed in the present study. The number of patients undergoing salvage surgery for recurrences following radiotherapy was low in the present study.

The retrospective study published by Ben Arie *et al* (25) reported the rates of secondary malignancy to be ~17% in patients with head and neck cancer, which is comparable to the findings of the present study. Han *et al* (26) reported that the primary tumour and nodal stages were considered as determinants of survival for lip SCC, which is also similar to the results observed in the present study. The composite clinical stage is another important prognostic factor associated with survival (15), as was also observed in the present study.

There are only a few studies available to date that have focussed on the treatment outcomes of patients with lip cancer. The present retrospective study on the outcomes of patients with SCC of the lip treated with radical intent highlights the fact that high cure rates can be obtained for lip cancer when treatment is administered at the early stages. The cure and local control rates reported in the present study were high, irrespective of whether patients were treated with radiotherapy or surgery for early stage SCC of the lip, as was also reported in the study by Gooris *et al* (27).

The main limitation of the present study was the bias associated with a retrospective study design. Data on the exact site of the tumour (whether it was a tumour of the upper or lower lip) and late morbidity data could not be obtained in the present study. In addition, a number of patients were lost to follow-up, and the follow-up information of only 76% of patients could be obtained for estimating the 4-year OS and DFS times, and rates at the time of analysis.

In conclusion, in the present retrospective study on 120 patients with carcinoma of the lip treated with radical radiotherapy (brachytherapy or EBRT) or surgery with or without adjuvant treatment, the 4-year DFS and OS rates were 69.1 and 86.7%, respectively. The findings of the present study indicate that the outcomes of patients with carcinoma of the lip are favourable when treatment is administered at the early stages. The salvage rates were poor following relapse after radiotherapy.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

GB performed the literature search, designed the study, collected and analysed the data, wrote the manuscript, prepared the tables and edited the manuscript. RR was involved in the design of the study and assisted with data collection and analysis. MR assisted with data collection, the preparation of the tables and in the editing of the manuscript. LMN assisted with the interpretation of the data, updating the patient follow-up information, and in the drafting of the manuscript and preparing tables. FN assisted with the analysis of the data and in the writing of the discussion. ST assisted with the study design and in the overall preparation of the manuscript. PSG assisted with the statistical analysis, and in the preparation of the figures and tables. CTK performed the literature search, designed the study and assisted with the writing and editing of the manuscript. GB and CTK confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Regional Cancer Centre (Thiruvananthapuram, India) and no separate ethics committee approval was obtained, as this is a retrospective analysis and all data that were analysed were collected as part of routine diagnosis and treatment. Patients were diagnosed and treated according to standard treatment guidelines; the study does not report the use of experimental or new protocols.

Patient consent for publication

Patient consent for the standard treatment had been taken prior to commencing treatment. No separate consent was taken for publication, as this is a retrospective analysis and all data that were analysed were collected as part of routine diagnosis and treatment. Patients were diagnosed and treated according to standard treatment guidelines.

Competing interests

The authors declare that they have no competing interests.

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