Original Article

RESULTS OF NODE POSITIVE ORAL CAVITY CANCER PATIENTS OF NORTH-EAST INDIA TREATED WITH SURGERY FOLLOWED BY ADJUVANT THERAPY: A RETROSPECTIVE STUDY

Bhaskarjyoti Talukdar[1,*], Jhilam Gautam[2], Navin Nayan[3], Jibon Sharma[4]

[1]Department of Statistics, Cotton University, Guwahati, Pincode-781001, District-Kamrup Metro, Assam, India,
E-mail ID: bhaskarphd13@gmail.com, bhaskar3333.bt@gmail.com, Phone Number: 8486498230, 6003152880
ORCID ID: 0009-0004-2768-7479

[2]Department of Hospital Based Cancer Registry, Indian Council of Medical Research, State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India. ORCID ID: 0009-0007-2864-2418, E-mail ID: jhilamgautam1993@gmail.com

[3]Department of Radiation Oncology, State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India
E-mail ID: doctornnayan@gmail.com

[4]Department of Radiation Oncology, State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India
ORCID ID: 0000-0003-3944-215, E-mail ID: sharma5jibon@gmail.com

***Corresponding Author:** Bhaskarjyoti Talukdar
Department of Statistics, Cotton University, Guwahati, Pincode-781001, District-Kamrup Metro, Assam, India,
E-mail ID: bhaskarphd13@gmail.com, bhaskar3333.bt@gmail.com, Phone Number: 8486498230, 6003152880
ORCID ID: 0009-0004-2768-7479

DOI: 10.47750/pnr.2022.13.03.183

Received: 03 December 2021 **Accepted:** 07 January 2022 **Published:** 02 February 2022

Abstract

OBJECTIVE: The objective of this study is to evaluate the pattern of failure and risk factors associated with the loco-regional or distant failure after surgery followed by adjuvant therapy in radically treated node positive oral cavity cancer patients of North-East India.

MATERIAL AND METHODS: All node positive oral cavity cancer at diagnosis treated with surgery followed by adjuvant therapy in the period of 2017 to 2018 (2 years data) at State Cancer Institute (SCI), Gauhati Medical College (GMC), Assam were included in the study. Retrospective data were analyzed to assess the pattern of failure (loco-regional/distant) and risk factors associated with this failure. Survival outcomes were also analyzed.

RESULTS: Total 39 node positive oral cavity cancer patients treated with surgery followed by adjuvant therapy. Median disease-free survival (DFS) was 27 months [Standard Error (S.E) =8.037, Confidence Interval (C.I) =11.247 – 42.753]. However, 20 (51.3%) patients developed local recurrence, 8 (20.5%) patients developed only neck node recurrence and 9 (23.1%) patients developed distant metastasis to lung. Only two patients remained disease free till the time of analysis.

CONCLUSION: The likelihood of recurrence is significant in locally advanced oral cavity cancer, particularly when nodes were positive at diagnosis. The median disease-free survival (DFS) in our study was just 27 months. More intensive treatment is necessary in order to increase the overall survival (OS) and DFS.

Keywords: Oral cavity cancer; Radiotherapy; Chemotherapy; Node positive oral cancer; Surgery; Median disease-free survival; Overall survival; Kaplan-Meier Plot.

1. INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide, with approximately 19.3 million new cases and 10.0 million deaths in 2020 [1]. Head and Neck Squamous Cell Carcinoma (HNSCC) accounts for 90% of all malignant disease in the head and neck region of the body. Tobacco and alcohol use have traditionally been the major risk factors for all HNSCC sub-sites [2].

Oral Cancer (OC) is a major problem in the Indian subcontinent where it ranks among the top three types of cancer in the country[3] . India has one third of OC cases in the world [4]. Age-adjusted rate of OC is high in India i.e., 20 per 100,000 population and accounts for over 30% of all cancers in the country [5].

Risk factors for oral cavity cancer includes all forms of tobacco, including cigarettes, beedi, pipes, cigars, and chewing (smokeless) tobacco, keeping tobacco quid inside mouth, Paan with betel nut/areca nut [6–8]. Alcohol also increases the risk

of oral cancer [9]. The risk of oral cancer is even higher in people who use both alcohol and tobacco [10]. Other risk factors include ill-fitting dentures or sharp teeth, diet, Human Papillomavirus (HPV), decreased immunity [11–15].

OC is managed by using one or a combination of the modalities like surgery, radiotherapy and/or chemotherapy [16]. Most early-stage oral cancers can be locally excised or treated with radiotherapy, with no or minimal functional and physical morbidity. Elective neck dissection to remove lymph nodes may be considered in selected cases. Postoperative radiotherapy is indicated in patients with positive or involved resected margins who are not candidates for re-excision.

Surgery followed by postoperative radiotherapy is the preferred modality for patients with deep infiltrative tumours and for those with bone infiltration. Postoperative concurrent chemo-radiation has been found to be superior in those with surgical margins showing cancerous changes, then radiotherapy alone. Primary radiotherapy, with or without chemotherapy, is a reasonable option for locally advanced tumours without bone involvement.

Despite the use of resection and postoperative radiotherapy, high-risk Squamous Cell Carcinoma (SCC) of the head and neck frequently recurs in the original tumour bed. Typically, local or regional disease recurs in 30 percent of patients, and distant metastases appear in 25 percent; the five-year survival rate is 40 percent [17]. Patients who have two or more regional lymph nodes involved, extra-capsular spread of disease, or microscopically involved mucosal margins of resection have particularly high rates of Local Recurrence (LR) (27 to 61 percent) and distant metastases (18 to 21 percent) and a high risk of death (five-year survival rate, 27 to 34 percent)[18] .Cooper et al [19] concluded in his study that high-risk patients with resected head and neck cancer, concurrent postoperative chemotherapy and radiotherapy significantly improve the rates of local and regional control and DFS.

In a study conducted by Daly et al [20], the authors found that Local-Regional Control (LRC) for SCC of the OC treated with Intensity-Modulated Radiation Therapy (IMRT) with or without surgery remains unsatisfactory. Definitive and postoperative IMRT have favorable toxicity profiles. A surgery-to-radiotherapy (RT) interval of < 6 weeks improves LRC. The predominant failure pattern was local, suggesting that both improvements in target delineation and radio-sensitization and/or dose escalation are needed.

Another study conducted by Chan et al [21], shows nearly a third (12/38) of LR recurrences at marginal or out-of-field following postoperative IMRT for Oral Cavity Squamous Cell Carcinoma (OCSCC). He concluded that postoperative IMRT following gross total surgical resection requires careful and comprehensive target volume delineation and larger volumes may be needed than the primary RT setting.

Tzu-Yu Lai et al [22] retrospectively reviewed the clinical data of 150 patients with lateralized OCSCC, including carcinoma of the buccal mucosa, gingiva and retromolar-trigone. All patients underwent radical surgery followed by postoperative RT with or without concurrent chemotherapy. It was found that Local in-field recurrence is the most common failure pattern in lateralized buccal-gingival cancer after postoperative RT. The infratemporal fossa is a risk area for marginal failure and should be encompassed adequately in the postoperative RT field. Extra-capsular spread and positive or close margin are predictors of LRC for lateralized OC. Patients exhibiting such adverse features require more aggressive treatment.

Thavarool et al [23] in his retrospective study on OC concluded that node positivity is the single factor affecting recurrence and survival. The OS and DFS is better in patients without lymph node involvement and in patients with early stage of cancer as compared to the patients with node involvement and in advanced stages.

A study conducted by Koyfman et al [24] found that rates of disease recurrence for patients with stage III/IV SCC-OC treated with surgery and adjuvant (chemo) radiation therapy are high. High grade, and recurrent, tumors were at higher risk of recurrence, while patients with margin positivity and/or Extra-Capsular Extension (ECE) were not. Intensification strategies and improved risk stratification based on genomic profiling is needed for this patient population.

Hosni A et al [25] investigated the impact of Lymph Node Ratio (LNR), number of positive nodes/total number of excised nodes on regional-only-failure, distant-only-failure and OS in OSCC. High LNR was associated with higher regional-only-failure/distant-only-failure and lower OS in his retrospective review of pN0-2 OSCC-patients (1994–2012) treated with curative-surgery with neck dissection ± postoperative radiotherapy (PORT) ± concurrent chemotherapy

In the present study, we investigated the pattern of failure (loco-regional/distant failure) in radically treated node positive oral cavity cancer.

2. MATERIALS & METHODS

2.1. PATIENTS

A Retrospective study was conducted in SCI, GMC with approval from Institutional scientific and ethical committee. Data collection was done from the hospital record. All node positive oral cavity cancer diagnosed and treated during the period of January 2017 to December 2018 were included in the study. Inclusion – Exclusion criteria were applied (Table 1). Node positivity was based on both clinical examination and radiological investigation [Computed Tomography (CT) Scan].

TABLE 1: INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA	EXCLUSION CRITERIA
• Histologically proven cases of oral cavity cancer treated with radical intent. • AJCC 8th Edition Stage III– IVB • Age < 70 years • Performance status (KPS ≥ 70% or ECOG ≤ 2)	• AJCC 8th Edition Stage IVC • Performance status (KPS < 70% or ECOG > 2) • Patients who failed to complete the treatment. • Prior History of double primary (h/o) cancer irradiation or chemotherapy • H/o double primary cancer.

2.2. SURGERY

All patients underwent surgery as the primary treatment. Types of surgery were based on the tumor extent. Adjuvant treatment was administered based on the post operative histo-pathological examination report.

Radiotherapy was given with cobalt-60 machine in a 2D conventional technique to a total dose of 60 Gray (Gy) (Dose was escalated to 66 Gy in margin positive cases). Shrinking field technique was used in all patients to spare the spinal cord after 46 Gy. All patients were assessed weekly for radiation induced toxicity.

Concurrent chemotherapy was also administered in patients with margin positive and ECE. Administered Concurrent chemotherapy was weekly platinum-based chemotherapy (Cisplatin/Carboplatin).

2.3. FOLLOW UP

All patients were examined weekly to monitor treatment related toxicities and general conditions. After completion of treatment, follow up was done at the interval of 2-3 months in the outdoor department. Follow up included clinical examination and CT scan neck.

Patient suspected of having metastatic disease on follow up were subjected to an appropriate investigation and were managed accordingly.

2.4. STATISTICAL ANALYSIS

Statistical analysis of data was done using Statistical Packages for Social Sciences (SPSS) and Disease-Free Survival (DFS) was calculated using Kaplan-Meier Plot Method.

3. RESULTS AND DISCUSSION

A total of 39 patients were included in the study. All patients were histologically proven case of node positive oral cavity cancer. Surgery was performed on all patients and based on final histo-pathological report adjuvant therapy of radiotherapy with or without concurrent chemotherapy was administered. Patient and tumour characteristics are listed in Table 2.

TABLE 2: PATIENTS AND TUMOR CHARACTERISTICS

AGE (YEARS)	**FREQUENCY**	**PERCENTAGE**
<45	6	15.4
≥45	33	84.6
Total	39	100.0
GENDER		
M	27	69.2
F	12	30.8
Total	39	100.0
RURAL/URBAN		
Rural	32	82.1
Urban	7	17.9
Total	39	100.0
SUB-SITE		
Buccal Mucosa	17	43.6
Gingivo-buccal Sulcus	11	28.2
Oral Tongue	7	17.9
Lower Lip	3	7.7
Floor Of Mouth	1	2.6
Total	39	100.0
PRE MORPHOLOGY		
Well Differentiated Squamous Cell Carcinoma (WDSCC)	11	28.2
Moderately Differentiated Squamous Cell Carcinoma (MDSCC)	26	66.7
Poorly Differentiated Squamous Cell Carcinoma (PDSCC)	2	5.1
Total	39	100.0
STAGE		
III	18	46.2
IVA	21	53.8
Total	39	100.0

In the post operative histo-pathological report (Table 3), node positivity was found only in 33 (84.6%) patients. Out of total 39 patients, only eleven (28.2%) patients had Extra-Capsular Extension (ECE). In two patients, there was positive resection margin.

TABLE 3: POST OPERATIVE CHARACTERISTICS

POST MORPHOLOGY	FREQUENCY	PERCENTAGE
Well Differentiated Squamous Cell Carcinoma (WDSCC)	18	46.2
Moderately Differentiated Squamous Cell Carcinoma (MDSCC)	19	48.7
Poorly Differentiated Squamous Cell Carcinoma (PDSCC)	2	5.1
Total	39	100.0
TUMOR SIZE		
<2	5	12.8
2-4	27	69.2
≥4	7	18.0
Total	39	100.0
LYMPH NODE STATUS		
Positive	33	84.61
Negative	6	15.39
Total	39	100.0
MARGIN STATUS		
Negative	37	94.9
Positive	2	5.1
Total	39	100.0
EXTRA-CAPSULAR EXTENSION		
No	28	71.8
Yes	11	28.2
Total	39	100.0
RECURRENCE		
Nodal	8	20.5
Local	20	51.3
Distant Metastasis	9	23.1
No Recurrence	2	5.1
Total	39	100.0

Treatment related toxicities were assessed during the treatment and on follow up. None of the patient developed > grade 2 toxicity. On further follow up, 20 (51.3%) patients developed local recurrence (In field recurrence), 8 (20.5%) patients developed only neck node recurrence and 9 (23.1%) patients developed distance metastasis to lung. Only two (5.1%) patients were disease free at the time of analysis.

Further, follow up data showed that median DFS was 27 months only [Standard Error (SE) =8.037, Confidence Interval (CI)=11.247 – 42.753]. Kaplan – Meier plot of DFS is shown in Figure 1. From the figure 1, we can conclude that the rate of survival is following a decreasing trend.

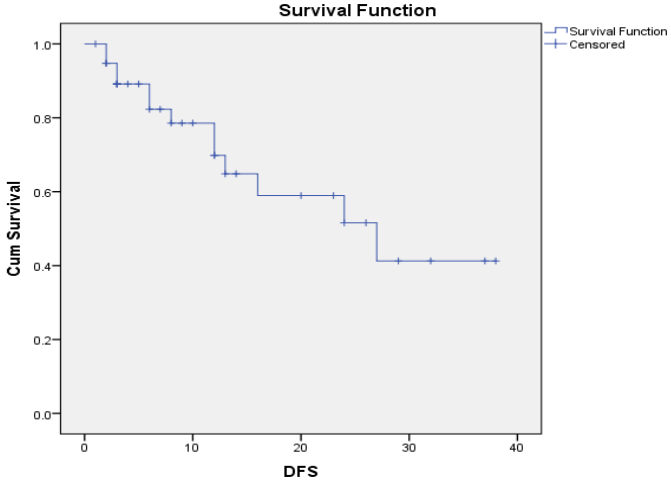

Figure-1: Kaplan-Meier Plot of Disease-Free Survival (DFS)

3.1. INTERPRETATION (FIGURE-1)

Here, N (Total Cases)	39
N of Events (Dead)	13
Censored N (Alive & Loss to Follow Up)	26(66.7%)

MEAN	
Estimates (in months)	23.858
Standard Error	2.84
Interval (Lower Bound)	18.291
Interval (Upper Bound)	29.424

MEDIAN	
Estimates (in months)	27
Standard Error	8.037
Interval (Lower Bound)	11.247
Interval (Upper Bound)	42.753

Here, Median DFS=27, from the figure, we can conclude that the rate of Survival is following a decreasing trend.

In the present study, we evaluated the clinical outcomes and recurrence pattern of radically treated node positive oral cavity cancer. The present data showed a high LR including neck nodal recurrence with modest median DFS of 27 months. There is paucity of data regarding pattern of failure in oral cavity cancers. In a respective analysis of 150 patients with lateralized OCSCC, including carcinoma of the buccal mucosa, gingiva and retromolar trigone, author concluded that Local in-field recurrence is the most common failure pattern in lateralized bucco-gingival cancer after postoperative RT [22]. Extra-capsular spread and positive or close margin are predictors of LRC for lateralized OC. Another recent study [26] evaluating pattern of failure in oral cavity cancer showed poorer OS (86.6% vs. 68.6%; p = 0.015) and DFS (86.5% vs. 74.9%; p = 0.01) with pathological positive node.
In the current study also 51.3% patients developed local recurrence i.e. in field recurrence. This indicates the high Loco-Regional Failure (LRF) rate in oral cavity cancer treated with surgery followed by adjuvant therapy. Median DFS of 27 months indicates that almost all patients failed at either loco-regional or distant site. Node positivity at diagnosis in oral cavity cancer has poor prognosis. Post-operative ECE and positive margin is another important prognostic marker in survival of these patients. This study was retrospective in nature.

4. CONCLUSIONS

The likelihood of recurrence is significant in locally advanced oral cavity cancer, particularly when nodes were positive at diagnosis. The median disease-free survival (DFS) in our study was just 27 months. More intensive treatment is necessary in order to increase the overall survival (OS) and DFS.
However, prospective study with large sample size may be required to validate the current study conclusion.

5. AKNOWLEDGEMENT

We would like to thank State Cancer Institute, Gauhati Medical College, Assam, for giving us this research opportunity.

6. CONFLICT OF INTEREST

The authors declare that there is no any conflict of interests.

7. FUNDING SOURCE

Nil

8. REFERENCES

1. Sung, H. *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* **71**, 209–249 (2021).
2. *Epidemiology, Pathogenesis, and Prevention of Head and Neck Cancer*. *Epidemiology, Pathogenesis, and Prevention of Head and Neck Cancer* (Springer New York, 2010). doi:10.1007/978-1-4419-1472-9.
3. Kalavathy Elango, J., Gangadharan, P., Sumithra, S. & Kuriakose, M. A. *Trends of Head and Neck Cancers in Urban and Rural India*. *Asian Pacific Journal of Cancer Prevention* vol. 7 (2006).
4. Coelho, K. R. Challenges of the oral cancer burden in India. *Journal of Cancer Epidemiology* Preprint at https://doi.org/10.1155/2012/701932 (2012).
5. Sankaranarayanan, R. *et al.* Effect of screening on oral cancer mortality in Kerala, India: A cluster-randomised controlled trial. *Lancet* **365**, 1927–1933 (2005).
6. Round, S. *TOBACCO SURVEY INDIA 2016-2017 | RepoRt*.

7. Pednekar, M. S., Gupta, P. C., Yeole, B. B. & Hébert, J. R. Association of tobacco habits, including bidi smoking, with overall and site-specific cancer incidence: Results from the Mumbai cohort study. *Cancer Causes and Control* **22**, 859–868 (2011).
8. Lin, W. J., Jiang, R. S., Wu, S. H., Chen, F. J. & Liu, S. A. Smoking, alcohol, and betel quid and oral cancer: A prospective cohort study. *J Oncol* (2011) doi:10.1155/2011/525976.
9. Lyon, F. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans VOLUME 96 Alcohol Consumption and Ethyl Carbamate*. (2010).
10. Znaori, A. *et al.* Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer* **105**, 681–686 (2003).
11. Son, Y. H. & Kapp, D. S. Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. *Cancer* **55**, 441–444 (1985).
12. *List of classifications by cancer sites with sufficient or limited evidence in humans, IARC Monographs Volumes 1-134 a Cancer site Carcinogenic agents with sufficient evidence in humans*. (2023).
13. Chocolatewala, N. M., Chaturvedi, P. & Rangoonwala, M. A. Free full text available from www.cancerjournal.net PMID: *****. *J Cancer Res Ther* **5**,.
14. Baverstock, K., Cardis, E., Guilmette, R. & Hill, M. A. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100. A Review of Human Carcinogens. Part D: Radiation Prostate cancer in the Cohort of Mayak Workers View project INWORKS View project*. https://www.researchgate.net/publication/254258381 (2012).
15. Grulich, A. E., van Leeuwen, M. T., Falster, M. O. & Vajdic, C. M. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* **370**, 59–67 (2007).
16. Sankaranarayanan, R., Ramadas, K., Amarasinghe, H., Subramanian, S. & Johnson, N. *Oral Cancer: Prevention, Early Detection, and Treatment*.
17. Laramore, G. E. *et al. American College of Radiology, I 101 Market St., 14th Fl., Philadelphia, PA 19107; 3Division of Hematology and Oncology*.
18. Cooper, J. S. *et al. PRECISELY DEFINING HIGH-RISK OPERABLE HEAD AND NECK TUMORS BASED ON RTOG #85-03 AND #88-24: TARGETS FOR POSTOPERATIVE RADIOCHEMOTHERAPY?* (1998).
19. Cooper, J. S. *et al*. *350;19 www.nejm.org may 6*. *n engl j med* vol. 350 www.nejm.org (2004).
20. Daly, M. E. *et al.* Intensity-modulated radiotherapy for oral cavity squamous cell carcinoma: Patterns of failure and predictors of local control. *Int J Radiat Oncol Biol Phys* **80**, 1412–1422 (2011).
21. Chan, A. K. *et al.* Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: Patterns of failure. *Oral Oncol* **49**, 255–260 (2013).
22. Lai, T. Y. *et al.* The pattern of failure and predictors of locoregional control in lateralized buccogingival cancer after postoperative radiation therapy. *Journal of the Chinese Medical Association* **80**, 569–574 (2017).
23. Thavarool, S. B. *et al.* Improved survival among oral cancer patients: Findings from a retrospective study at a tertiary care cancer centre in rural Kerala, India. *World J Surg Oncol* **17**, (2019).
24. Koyfman, S. A. *et al.* Patterns of Failure and Factors Associated With Disease Recurrence in Patients With Stage III/IV Squamous Cell Carcinoma of the Oral Cavity (SCC-OC) Treated With Surgery and Postoperative (Chemo)radiation Therapy. *International Journal of Radiation Oncology*Biology*Physics* **88**, 482 (2014).
25. Hosni, A. *et al.* Lymph node ratio relationship to regional failure and distant metastases in oral cavity cancer. *Radiotherapy and Oncology* **124**, 225–231(2017)