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Research Article

Survival Outcomes in Patients with N3b Nodal Disease in Oral Cavity Squamous Cell Carcinoma: A Single Institutional Study

Monalisa Banerjee[1], Ankit Gupta[1], Shehnaz Kantharia[2] and Rajesh Kantharia[1]*

[1]Department of Head and Neck Oncosurgery, Kailash Cancer Hospital and Research Centre, Muni Seva Ashram, Goraj, India

[2]Department of Otorhinolaryngology/Head and Neck Oncosurgery, Kailash Cancer Hospital and Research Centre, Muni Seva Ashram, Goraj, India

***Corresponding Author:** Rajesh Kantharia, Department of Head and Neck Oncosurgery, Kailash Cancer Hospital and Research Centre, Muni Seva Ashram, Goraj, India.

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Abstract

Aim: Oral cavity cancers have high propensity for lymphatic dissemination which strongly influences the prognosis and reduces survival by 50%. This study aims to estimate the survival outcomes of patients operated for Oral Cavity Squamous Cell Carcinoma with N3b nodal disease.

Methodology: Retrospective analysis of prospectively collected data of final histopathology report of patients operated for advanced Oral Cavity Squamous Cell Carcinoma with N3b nodal disease from January 2018 to January 2020 was done. Out of the 113 patients, 55 patients were included in this study. Patients with incomplete treatment and follow ups were excluded. The demographic details, tumor sub-sites, tumor stage, nodal stage, adjuvant treatment received, type of neck dissection and nodal yield were analyzed. The primary end point of the study was to assess the overall survival and Disease free survival.

Results: The total number of neck dissections performed, were 55, of which modified neck dissection (MND) were 30 and supraomohyoid neck dissection (SOHD) were 25. Overall survival data of patients were found to be ≤6 months in 7 patients (12.7%), 7months - 1year in 15 patients (27.27%), 1.1-2 years in 16 patients (29.09%), 2.1-3 years in 13 patients (23.63%) and >3 years in 4 patients (7.27%).

Conclusion: Node positivity is the single most important detrimental factor of survival in Oral cavity squamous cell carcinoma and the worst prognosis group is patients with N3b nodal disease and advanced T stage.

Keywords: Extra Nodal Extension; N3b Node; Survival Outcome; Neck Dissection; Prognosis; Squamous Cell Carcinoma

Abbreviations

ENE: Extra Nodal Extension

Introduction

Oral cavity cancers have high propensity for lymphatic dissemination which strongly influences the survival and prognosis. The presence of even a single metastatic node categorizes the patient in stage III/IV and reduces survival by 50% [1]. The American Joint Committee on Cancer (AJCC) Staging has incorporated several factors to account for nodal disease, which specifically includes size, laterality, and number of malignant nodes.

Recent changes in the AJCC 8th Edition also factor in extranodal extension (ENE), also known as extracapsular spread. The term Extra Nodal Extension is defined as an extension of tumour cells through the LN capsule into the perinodal adipose tissue. According to the current TNM classification, ENE in even a single node upstages the patient to stage IVA or IVB [3]. ENE has become a major determinant in the intensification of adjuvant treatment by addition of chemotherapy concurrently to radiotherapy [4-6]. It has been observed in various studies that there is a definite survival benefit by adding chemotherapy to adjuvant radiotherapy [7]. Several studies have investigated the survival outcomes of N3b nodal diseases in various sub-sites of the head and neck region but not exclusively for oral cavity. This study aims to estimate the survival outcomes of patients operated for Oral Cavity Squamous Cell Carcinoma with N3b nodal disease.

Materials and Methods

Patients and treatment

A retrospective analysis of prospectively collected data of surgically treated patients of oral squamous cell carcinoma with N3b nodal disease on final histopathology report was done from January, 2018 to January, 2022 at Kailash Cancer Hospital and Research Centre, Muni Seva Ashram, Goraj. Pre operative evaluation included careful physical examination and contrast enhanced computed tomography (CECT),magnetic resonance imaging (MRI) or PET CT. Patients with histopathologically confirmed N3b nodal disease received adjuvant treatment as per standard guidelines and were followed up according to the NCCN Guidelines 2022. Out of the 113 patients, 55 patients were included in this study. Patient who underwent salvage surgery for recurrences, post NACT patients, and patients who were lost to follow up were excluded. The demographic details, tumor sub-sites, tumor stage, nodal stage, type of neck dissection and nodal yield were analyzed. In all patients analyzed, supra omohyoid neck dissection (level I-III) was performed for N0 neck and modified radical neck dissection (level I-V) was performed for N+ neck. The necessity of ressecting adjacent tissues (e.g. the internal jugular vein, spinal accessory nerve and sternocleidomastoid muscle) was determined preoperatively or intra-operatively based on clinical examination, doppler, or intra-operative findings. All LNs were sampled and paraffin embedded in toto. Haematoxylin–eosin-stained slides were microscopically analyzed for the presence of tumour tissue and for extra nodal extension. The presence of ENE was defined as any breach of the lymph node capsule. Microscopic measurement of the grossed lymph node specimens was done. The total number of nodes with ENE, the extent of ENE, total number of positive nodes and levels of positive nodes were analyzed. In case of multiple nodes presenting with ENE, the node with the maximum ENE was considered.

Results

Statistical analysis

Kaplan Meier statistical analysis was used to determine the overall survival and disease free survival outcomes and the association between stage of the disease with DFS and OS.IBM SPSS statistics version 23.0 was used for analysis.

The total number of patients, included in the study were 55 out of which 42 were males and 13 females. The total number of neck dissections performed were 55, of which modified neck dissection (MND) were 30 and supraomohyoid neck dissection (SOHD) were 25. Patients with disease of the alveolo-buccal complex sub-site were 34(61.8%) and those involving the tongue were 21 (38.1%) pTNM Staging was T1 = 1(1.81%), T2 = 9(16.3%), T3 = 25(45.4%) and T4 = 20 (36.4%). In the final histopathology report of neck dissection specimen, the number of positive nodes was 1 in 2 patients, 2 in 14 patients, 3 in 16 patients, 4 in 6 patients, 5 in 6 patients and >5 in 11 patients (Figure 1) and size of the N3b nodes were found to be <10 mm in 1, 11-20 mm in 30, 21-30mm in 15, 31-40mm in 7 and >40 mm in 2 (Table 1).

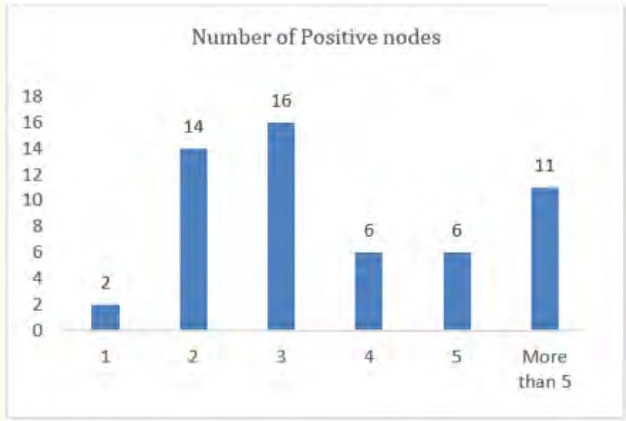

Figure 1: Frequency chart depicting the number of positive nodes was 1 in 2 patients, 2 in 14 patients, 3 in 16 patients, 4 in 6 patients, 5 in 6 patients and >5 in 11 patients (Figure 1).

Size of the nodes	Frequency	Percent	Valid Percent	Cumulative Percent
Less than 10	1	1.8	1.8	96.4
11-20	30	54.5	54.5	54.5
21-30	15	27.3	27.3	81.8
31-40	7	12.7	12.7	94.5
More than 40	2	3.6	3.6	100.0
Total	55	100.0	100.0	

Table 1: Size of the N3b nodes were found to be <10 mm in 1 patient, 11-20 mm in 30 patients, 21-30 mm in 15 patients, 31-40 mm in 7 patients and >40 mm in 2 patients.

All 55 patients received adjuvant CTRT according to the standard institutional protocol. A total dose of 66-70 Gy of adjuvant radiation therapy, in 33-35 fractions along with 6 cycles of chemotherapy was administered. The chemotherapy regimen was: Cisplatin 30-40 mg/m2 once a week.

The primary end point of the study was to assess the overall survival and disease free survival. Overall survival data was calculated from the date of completion of treatment till the last date of follow up and disease free survival was calculated from the date of completion of treatment up to the day of diagnosis of locoregional recurrence, second primary or distant metastasis. Overall survival data of patients were found to be ≤6 months in 7 patients (12.7%), 7 months - 1 year in 15 patients (27.27%), 1.1-2 years in 16 patients (29.09%), 2.1-3 years in 13 patients (23.63%) and > 3 years in 4 patients (7.27%). Univariate survival analysis was performed to compare the overall survival and disease free survival with the T stage of the disease. The probability of survival was found to be maximum for T1 diseases and there was a decrease in the trend of probability of survival with the increase in T stages. Mantel-cox analysis was applied to test the equality of survival distribution according to T stages which although was not significant showed a variability in the probability of survival which was maximum in T1 disease and decreased with the increase in staging to T2, T3, T4. (p = .243) figure 2,3 and table 2.

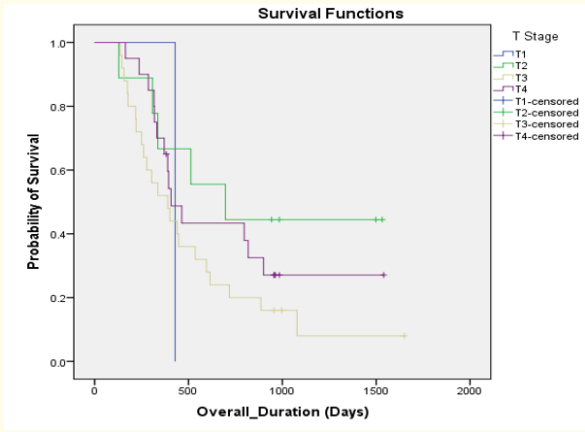

Figure 2: Line graph showing overall survival which was maximum in T1 disease and decreased with the increase in staging to T2, T3, T4.

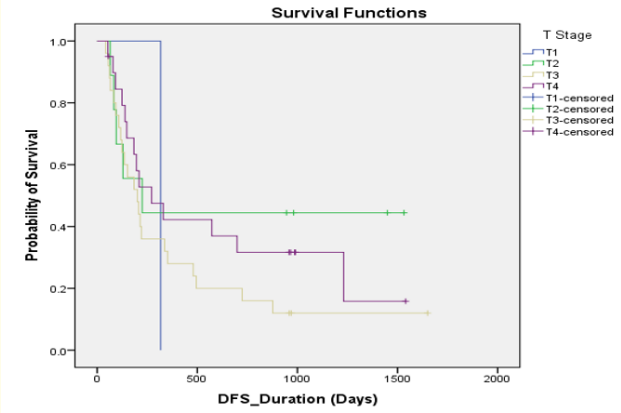

Figure 3: Line graph showing disease free survival which was maximum in T1 disease and decreased with the increase in staging to T2, T3, T4.

T Stage	Total N	N of Events	N	Percent
T1	1	1	0	0.0%
T2	9	5	4	44.4%
T3	25	22	3	12.0%
T4	20	14	6	30.0%
Overall	55	42	13	23.6%

Table 2: Depicting total number of patient's having T1, T2, T3 and T4 a stages of disease were 1, 9, 25 and 20 respectively.

Another comparison was done based of the nodal yield and probability of survival. Survival analysis was done by comparison of lymph node ratio with overall survival and disease free survival. A median lymph node ratio cut off of .20 was chosen depending on the variability of the data analyzed, and we have observed a higher probability of survival for nodal yield <.20 in comparison with those >.20. Hence there is a decrease in probability of survival with increase in nodal yield and lymph node ratio of the neck dissections specimen. Mantel-cox (p = .367) and Generalized Wilcoxon (p = .706) analysis was used which has been depicted in figure 4,5 and table 3.

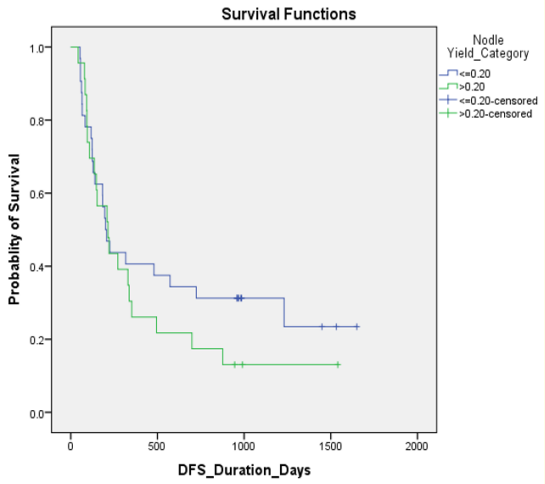

Figure 4: Depicting a higher probability of disease free survival for nodal yield <.20 in comparison with those >.20.

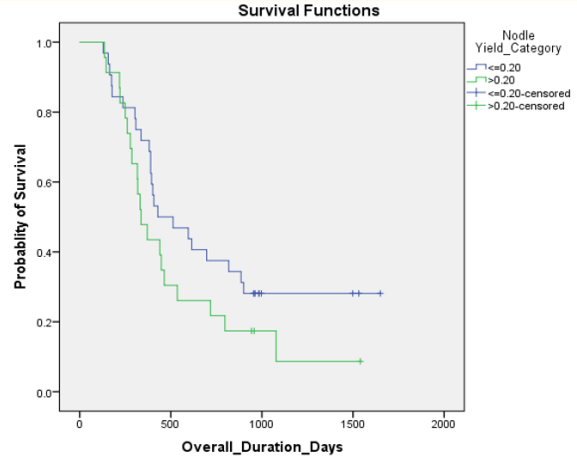

Figure 5: Depicting a higher probability of overall free survival for nodal yield <.20 in comparison with those >.20.

Nodle Yield_ Category	Total N	N of Events	Censored	
			N	Percent
<=0.20	32	23	9	28.1%
>0.20	23	20	3	13.0%
Overall	55	43	12	21.8%

Table 3: Depicting A median lymph node ratio cut off of .20 was chosen depending on the variability of the data analyzed, and so that both the groups had almost similar number of subjects for comparison.

Discussion

Extra Nodal Extensionis defined as the tumor's ability to locally invade the lymph node capsule [8]. This occurs by invasion of the tumor cells into the perinodal adipose tissue after the tumor cells have invaded into the lymphatics. This phenomenon is associated with increased tumor aggressiveness and metastatic potential. In the American Joint Committee on Cancer TNM staging, N stage considers the size of lymph nodes, laterality and number of nodes. The recent 8th edition of the AJCC has modified the nodal staging by incorporating extranodal extension (ENE); those with ENE in nodes smaller than 3 cm are classified as N2a and those larger than 3 cm are classified as N3b. Incorporation of ENE was intended to convey the aggressiveness and prognosis of the disease [2,9,10]. This aggressive tumor biology has always been associated with poor survival outcomes [11]. In locally advanced head and neck squamous cell carcinoma, extra nodal extension has long been considered a pathologic high-risk feature, meaning that patients are at increased risk of disease progression and would benefit from the addition of chemotherapy to adjuvant radiotherapy. In the present observational study, all patients with N3b disease received adjuvant CTRT after appropriate resection and were followed up for Overall Survical (OS) and Disease Free Survival (DFS). At the end of 3 years, the overall survival was 7.21%. This is in affirmation with the study by JA Woolgar., *et al.* [12] which has shown a sharp decrease in the overall survival with the presence of ENE, irrespective of it being microscopic or macroscopic. The author has also quoted ENE is a more important predictive factor for survival than margin positivity. In a study by Kalnins I.K., *et al.* [13], survival according to capsular penetration has been discussed much before the advent of the term extra nodal extension came into existence which showed, five year survival was 29 per cent

(62/213) for patients with histologically positive lymph nodes. If the capsule was intact, five year survival was 33 per cent (54/162). If the lymph node capsule was penetrated microscopically only, five year survival was 28 per cent (4/14). If soft tissue spread had occurred, five year survival was 11 per cent (4/37).

In our study, when survival outcomes were compared with the T stage, it was found that the survival outcomes dropped with the increase in the T stage. A similar study has been quoted by Dong-Ho Geum., *et al.* [14] which shows a decreasing trend in the overall survival and disease free survival with the increase in the T stage in oral squamous cell carcinoma.

Another parameter of this study was to look at the relation and influence of Lymph node ratio with the survival outcomes. The Lymph Node Ratio is defined as the ratio of metastatic nodes to the total number of harvested lymph nodes, and it has emerged as an indicator of cancer-specific survival in recent years. In our study, 0.20 was taken as a baseline reference point as it was found that there was a significant decrease in survival outcomes lymph node ratio >0.20 as compared to lymph node ratio <0.20 depending on the variability of the data analyzed, and so that both the groups had almost similar number of subjects for comparison and to reduce bias.

Few studies analyzed LNR in patients with different head and neck cancer. Gil., *et al*. [15] analyzed 386 oral cavity cancer patients who received primary surgery with or without adjuvant radiotherapy and showed LNR remained the only independent predictor of OS (HR = 2.0, p = 0.02), disease specific survival (DSS) (HR = 2.3, p = 0.02), and local control (HR = 4.1, p = 0.005). Kim., *et al*. [16] analyzed 211 oral cavity cancer patients who underwent surgery and found that LNR was an independent predictor of DSS (HR = 3.24, 95% CI = 1.61–6.53; p = 0.001. The cutoff value for LNR varied across studies. Gil., *et al*. [15] used a cutoff value of 0.06. Sayed., *et al*. [17] reviewed medical data of 1408 oral cancer patients and found LNR (0.088) was significantly associated with survival outcomes. Hua., *et al*. [18] analyzed 81 hypopharyngeal cancer patients and revealed that those with an LNR ≧ 0.1 had poor OS.

This retrospective study had some limitations. Several patients had lost to follow up or had irregular follow up and hence had to be excluded from the study thus lesser number of patients were included in the study. However, further study is needed to confirm the prognostic value of LNR in head and neck cancer patients.

Conclusion

Node positivity, N3b nodal disease, higher Lymph Node Ratio, and advanced T stages still remain the worst prognostic factors for overall survival and disease free survival in Oral squamous cell carcinoma.

Conflict of Interest

The authors declare that they have no conflict of interest.

Bibliography

1. Huang Shao Hui., *et al*. "Assessment criteria and clinical implications of extranodal extension in head and neck cancer". *American Society of Clinical Oncology Educational Book* 41 (2021): 265-278.

2. Byrd, David R., *et al*. AJCC cancer staging manual. Eds. Mahul B. Amin, Stephen B. Edge, and Frederick L. Greene. New York: springer, 1024 (2017).

3. Brierley James D., *et al*. TNM classification of malignant tumours. John Wiley and Sons (2017).

4. Cooper Jay S., *et al*. "Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck". *New England Journal of Medicine* 350.19 (2004): 1937-1944.

5. Bernier Jacques., *et al*. "Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer". *New England Journal of Medicine* 350.19 (2004): 1945-1952.

6. Bernier Jacques., *et al*. "Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (# 22931) and RTOG (# 9501)". *Head and Neck: Journal for the Sciences and Specialties of the Head and Neck* 27.10 (2005): 843-850.

7. Forastiere Arlene A., *et al*. "Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer". *Journal of clinical Oncology* 31.7 (2013): 845-852.

8. Mamic M., *et al*. "Prognostic significance of extranodal extension in oral cavity squamous cell carcinoma with occult neck metastases". *International Journal of Oral and Maxillofacial Surgery* 50.3 (2021): 309-315.

9. Zanoni, Daniella Karassawa *et al*. "Changes in the 8th Edition of the American Joint Committee on Cancer (AJCC) Staging of Head and Neck Cancer: Rationale and Implications". *Current Oncology Reports* 21.6 (2016): 52.

10. Lydiatt WM., *et al*. "Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual". *CA Cancer Journal of Clinics* 67.2 (2017): 122-137.

11. Bhattacharya Priyanka and Rajarshi Mukherjee. "Lymph node extracapsular extension as a marker of aggressive phenotype: Classification, prognosis and associated molecular biomarkers". *European Journal of Surgical Oncology* 47.4 (2021): 721-731.

12. Woolgar J A., *et al*. "Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread". *Oral Oncology* 39.2 (2003): 130-137.

13. Kalnins Inars K., *et al*. "Correlation between prognosis and degree of lymph node involvement in carcinoma of the oral cavity". *The American Journal of Surgery* 134.4 (1977): 450-454.

14. Geum Dong-Ho., *et al*. "The impact factors on 5-year survival rate in patients operated with oral cancer". *Journal of the Korean Association of Oral and Maxillofacial Surgeons* 39.5 (2013): 207.

15. Gil Ziv., *et al*. "Lymph node density is a significant predictor of outcome in patients with oral cancer". *Cancer: Interdisciplinary International Journal of the American Cancer Society* 115.24 (2009): 5700-5710.

16. Kim SY., *et al*. "Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma". *Annals of Surgery Oncology* 18 (2011): 2310-2317.

17. Hua Yong-hong., *et al*. "Effect of number and ratio of positive lymph nodes in hypopharyngeal cancer". *Head and Neck* 37.1 (2015): 111-116.

18. Sayed Suhail I., *et al*. "Can metastatic lymph node ratio (LNR) predict survival in oral cavity cancer patients". *Journal of Surgical Oncology* 108.4 (2013): 256-263.