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ROLE OF LYMPH NODE RATIOIN PREDICTING RECURRENCEIN BUCCAL MUCOSAL CANCERSAFTER NEO-ADJUVANT CHEMOTHERAPY

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ABSTRACT

Introduction: Lymph node ratio as a prognostic marker remains under- evaluated as a prognostic marker in the neo-adjuvant setting. We aim to investigate its utility as a prognostic marker in locally advanced buccal mucosal cancers undergoing surgery after receiving neo- adjuvant chemotherapy.

Methodology: 125 patients of T4b buccal mucosal squamous cell carcinomas received neoadjuvant chemotherapy. Responders to chemotherapy underwent curative resections and were included in the study. Histopathology reports were analysed for total lymph node yield from the neck dissections and lymph node ratio, which was correlated with clinical outcomes.

Results: 61 patients showed at least a partial response to chemotherapy and underwent surgery. 33% patients had positive neck nodes. Average lymph node yield was 23.63 (+/- 7.37). Average lymph node ratio in node positive patients was 0.073 (+/- 0.1). 18.03% patients had a recurrence over a 2 year follow up period. Average lymph node ratio in patients with recurrence and those without was 0.073 (+/- 0.1) and 0.07 (+/- 0.097) respectively.

Conclusion: Lymph node ratio does not show promise as a prognostic marker in locally advanced buccal mucosal cancers undergoing surgery after neo-adjuvant chemotherapy.

KEYWORDS : Lymph node ratio, buccal mucosa cancer, neck dissection, neo-adjuvant chemotherapy.

INTRODUCTION

With an estimated 3,00,000 new cases and 1,28,000 deaths per year, squamous cell carcinoma of the oral cavity (OSCC) is among the most common malignant tumors and a significant source of morbidity. Although the presence of lymph node metastases has been associated with poor outcome, nodal stage by itself was not shown to reliably predict prognosis. As limited lymph node dissection may result in pathological under staging, lymph node density (LND) has emerged as an independent prognostic factor for OSCC. Lymph node density, or lymph node ratio (LNR), equals the ratio of positive lymph nodes to the total number of excised lymph nodes. This ratio assesses both aspects of neck disease; nodal metastases as well as adequacy of surgical clearance of the lymph node basins.Existing literature provides evidence for lymph node ratio as a prognostic marker, as well as a decision making tool for adjuvant therapy in patients undergoing upfront surgery, however, its evaluation as a prognosticating tool in the neoadjuvant setting is lacking. We aim to investigate the utility of lymph node ratio as a prognostic marker for disease recurrence in locally advanced buccal mucosa cancers undergoing surgery after receiving neoadjuvant chemotherapy.

METHODOLOGY

A total of 125 patients of T4b buccal mucosal squamous cell carcinomaswerescreened for inclusion in this study during the year 2016- 2017. Staging was done by a thorough clinical examination and a contrast enhanced CT scan. All patients received neo-adjuvant chemotherapy after an institutional multidisciplinary panel discussion. Response evaluation was performed two weeks after completion of chemotherapy.Patients with a partial or complete clinical response of the primary tumour were taken for surgery and included in the analysis. Patients with no response to chemotherapy or with progressive disease were palliated, and excluded from the analysis.

Most patients received a combination of paclitaxel and carboplatin in doses of 175 mg/m2 and AUC 5 – 7.5 respectively. Either 2 or 3 doses of induction chemotherapy were given based on response. Other chemotherapy regimens given were Paclitaxel, Carboplatin and 5-fluorouracil combination (TPF regimen) and the Cisplatin with Methotrexate combination. The decision as to the type of chemotherapy to be administered was taken by the Medical Oncologist.

Surgery included an R0 resection of the primary tumour with wide margins, with the extent of mandibulectomy and upper alveolectomy dictated by the extent of the tumour. Neck was treated in accordance with standard guidelines.

Histopathology reporting was done in a standard proforma based manner. Lymph node ratio was calculated by dividing the number of positive nodes by the total number of nodes dissected.

Adjuvant therapy consisted of External Beam Radiation 60 Gy in 30 fractions given over 6 weeks at the rate of 2 Gy/fraction for 5 days/week followed by 2 day rest. Addition of concurrent chemotherapy was reserved for patients with positive margins or extra nodal extension.

Follow up schedule consisted of monthly visits for the first 6 months, 2 monthly visits for the next 6 months and 3 monthly for the second year of follow-up. Contrast enhanced CT scan of the region was performed at the 6th month of follow-up followed by the 1st year and end of 2nd year. Imaging of other regions (eg. Chest) were done on basis of clinical suspicion.

RESULTS

125 patients of cT4b buccal mucosal cancers with varying cN stages received neoadjuvant chemotherapy over the course of 1 year. Of these, 61 patients were responders and underwent surgery. These patients were included in the analysis, and will henceforth be referred to as the study population. Patients who were ineligible for surgery after response evaluation were excluded from the study.

The demographic characteristics of the study populationare summarized in Table 1.

Table 1.

Demographic characteristic	
Total number	61
Age in years	46.73 +/- 10.22
Sex distribution	
Males	51 (83.6%)
Females	10 (16.4%)
Addictions	
None	6 (3.66%)
Tobacco	52 (85.2%)

Tobacco and alcohol	3 (4.91%)
cN stage	
cN0	48 (78.8%)
cN1	7 (4.27%)
cN2	5 (3.05%)
cN3	1 (0.61%)

Chemotherapy and response evaluation data is summarized in Table 2.

Table 2.

Chemotherapy regimen	Number of patients
2 cycles P + C*	11 (18.03%)
3 cycles P + C*	48 (78.68%)
3 cycles TPF**	2 (3.27%)
Chemotherapy response	
Complete clinical response	1 (1.63%)
Partial response***	37 (60.65%)
Less than partial response	23 (37.7%)

*P+C- Paclitaxel + Carboplatin
**TPF- Paclitaxel + Carboplatin + 5-Fluorouracil
***Partial response defined as at least 50% reduction in primary tumour volume and at least stable neck disease.

Average lymph node yield was 23.63 (+/- 7.37). 33 (54%) patients had positive lymph nodes. Extra-nodal extension was present in 22 (36.06%) patients. Lympho-vascular invasion was present in 6 (9.83%) patients. Peri-neural invasion was present in 12 (19.67%) patients. Average number of positive nodes was 1.61 (+/- 2.02). Average lymph node ratio in node positive patients was 0.073 (+/- 0.1).Lymph node ratio in node positive patients ranged from 0.026 to 0.421. Distribution of node positive patients according to lymph node ratio is summarized in Table 3.

Table 3.

Lymph node ratio	Number of patients
<0.05	6 (18.18%)
0.05- 0.1	8 (24.24%)
0.2	12(36.36%)
>0.2	5 (15.15%)

11 (18.03%) patients had a loco- regional recurrence over a follow- up period of 2 years.Average lymph node ratio in node positive patients with a recurrence was 0.073 (=/- 0.1). Comparison between recurrent and non- recurrent patients is shown in Table 4.

Table 4.

Characteristic	Patients with recurrence	Patients without recurrence
Number	11(18.03%)	50(81.96%)
Tumour grade		
Well differentiated	0	14(28%)
Moderately differentiated	10 (90%)	35(70%)
Poorly differentiated	1 (10%)	1(2%)
cN stage		
cN0	8 (72.72%)	40 (80%)
cN1	2 (18.18%)	5 (10%)
cN2	1 (9%)	4 (8%)
cN3	0	1 (2%)
Clinical response assessment		
Complete response	0	1 (2%)
Partial response	5 (45.45%)	33 (66%)
Less than partial response	6(54.54%)	16 (32%)
ypT stage		
ypT0	1 (10%)	1 (2%)
ypT1	0	1 (2%)
ypT2	0	4 (8%)
ypT3	0	1 (2%)
ypT4a	0	1 (2%)
ypT4b	10 (90%)	42 (84%)
ypN stage		
ypN0	2 (18.18%)	26 (52%)
ypN1	3 (27.27%)	9 (18%)
ypN2b	6 (54.54%)	15 (30%)
Average lymph node yield	23.83 (+/- 7.38)	23.71 (+/- 7.4)
Average Lymph node ratio (in node positive patients)	0.073 (+/- 0.1)	0.07 (+/- 0.097)
Lymph node ratio distribution		
<0.05	2 (22.22%)	5 (20.83%)
0.05- 0.1	2 (22.22%)	6(25%)
0.1- 0.2	2 (22.22%)	11(45.83%)
>0.2	3 (33.33%)	2(8.33%)
LVI	3 (27.27%)	3(6%)
PNI	3 (27.27%)	9 (18%)
ENE	6(54.54%)	15 (30%)
Average closest margin (cm)	0.38 (+/- 0.09)	0.44 (+/- 0.2)

DISCUSSION

The adequacy of lymph node clearance was equal in patients with or without a recurrence since the average lymph node yield in both groups was similar (23.83 and 23.71 respectively).The lymph node ratio, contrary to expectations, was of no significance in predicting a recurrence. It was observed to be similar in both subsets (0.073 and 0.07 respectively). A possible explanation for this finding could be the down-staging of disease burden in the neck due to the administration of neo-adjuvant chemotherapy, leading to lower lymph node ratios in patients who may have had a higher percentage of positive neck nodes had they undergone surgery prior to receiving chemotherapy. Findings from other studies supporting lymph node ratio as a prognostic factor have investigated it only in the upfront surgery setting. The value of lymph node ratio may lie in determining appropriate adjuvant therapy after surgery.

There was no difference in T stage or disease burden in the neck prior to chemotherapy in either groups. However, a significantly higher proportion of patients with recurrence had a higher stage residual nodal disease after chemotherapy as compared to those without a recurrence. Also, a higher percentage of patients with recurrences had less than 50% reduction in tumour size after chemotherapy. The degree of response to chemotherapy seems to be more predictive of clinical outcomes than the initial disease status in locally advanced buccal mucosa cancers and is an area of potential study.

A higher proportion of patients who did not have a recurrence had well differentiated tumours as opposed to those who had a recurrence. Also, high risk features, namely lympho-vascular invasion, peri-neural invasion and extra- nodal extension were present in a higher proportion of patients who had a recurrence, suggesting that tumour biology plays a highly important role in disease recurrence, and eventually clinical outcomes.

CONCLUSION

Lymph node ratio is not predictive of recurrence in patients undergoing surgery after having received neo-adjuvant chemotherapy. Response to chemotherapy, tumour differentiation, and extra-nodal extension are more relevant prognostic indices in the neo-adjuvant setting for locally advanced buccal mucosal cancers.

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