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Original Article

Can Metastatic Lymph node ratio be used as an independent prognostic factor in Carcinoma tongue

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Abstract

Background: Lymph node metastasis is an established prognostic factor in carcinoma of tongue. The association between lymph node ratio (LNR, the ratio of positive lymph nodes to the total number of dissected lymph nodes) and survival has been recently studied. But the available literature is mostly retrospective in nature and they take the broad group of oral squamous cell carcinoma as a whole and not as a single sub–site; also it does not take in to consideration the importance of standardising the minimum number of lymph nodes to be dissected or a single head and neck pathologist examining the specimen to avoid wide variations in the ratio and to reduce the bias. Hence we sought to determine using a prospective study whether the lymph node ratio, as an independent factor impacts survival in node–positive squamous cell carcinoma of tongue and whether a cut–off can be arrived at to risk stratify the patients.

Methods: We prospectively studied 51 consecutive pathologically node positive patients with squamous cell carcinoma tongue who satisfied our selection criteria. A standard surgery for the primary was done under frozen control and a comprehensive neck dissection, with the minimum number of lymph node harvest kept at 15. All the specimens were examined by a single head and neck pathologist. Further adjuvant treatment was given according to our institution protocol. They were followed up with a regular clinical examination for an average period of 24 months. The 2 Yr OS and DFS were calculated using the Kaplan Meier method. LNR was subjected to univariate and multivariate analyses.

Results: The 2 yr OS was 37.8 % for patients with LNR > 0.10 compared with 88.2 % for patients with LNR <0.10 (p value=0.0187). Similarly, the DFS was 46.3% for patients with LNR > 0.10 compared with 83.6% for those with LND<0.10 (p value=0.0859). LNR was a significant prognostic factor in both univariate and multi variate analyses.

Conclusion: In squamous cell carcinoma of tongue, an increased Lymph node ratio (LNR) is a strong predictor of decreased survival. A lymph node ratio (LNR)> 0.10 is associated with a worse outcome.

Keywords: Squamous cell carcinoma, tongue, lymph node, ratio, prognosis

Introduction

Oral cavity cancer is the second most common cancer among males in our institute. Of which Squamous cell carcinoma of tongue accounts for majority of cases. Occult metastasis to the neck may occur in up to 34% of patients with squamous cell carcinomas of the oral cavity and as a result neck dissections are often performed prophylactically for both its prognostic value and also for its therapeutic implications. Nodal positivity, perineural invasion, lympho vascular emboli and extra capsular spread are established indications for adjuvant treatment (either radiotherapy alone or along with chemotherapy). The identification of metastatic lymph nodes is based on two factors 1) the number of lymph nodes dissected 2) adequate sampling by the pathologist. Hence both the surgical expertise and pathological scrutiny are essential to identify positive lymph nodes and hence adequately stage the patient. The lymph node ratio (LNR) attempts to compensate for this potential bias by arriving at a ratio of the number of positive lymph nodes to the total number of lymph nodes dissected rather than only taking the absolute number of positive lymph nodes in to consideration. Hence the LNR can be a better prognostic indicator.

The current TNM staging system for Oral Squamous cell carcinoma (OSCC) is based on primary tumour classification (T), nodal metastases (N) according to size,
number and distribution, and on the presence of distant metastases (M). In this staging system, the presence of lymph node metastases has been associated with poor outcome. However, it was later learnt that nodal stage by itself was not shown to reliably predict prognosis. Moreover, certain sub--sites in oral cavity have greater propensity for nodal metastasis, and hence a generalisation of the LNR for all sub--sites may not be acceptable. Hence the need for a better prognostic indicator which is specific for a sub--site should be arrived upon to help in staging and also in risk stratification.

**Materials and methods:**

We conducted the study in the Division of Surgical Oncology, Head and Neck unit at Regional Cancer Centre, Thiruvananthapuram. The proposal was presented to the Institutional review board and clearance was obtained. The recruitment period was for a period of one year i.e. June 1st 2012 to May 31st 2013. It included patients with histologically proven primary cases of Squamous cell Carcinoma of the tongue (anterior 2/3rd), N1, N2 status (pathological), ECOG performance status of 0, 1, or 2. Patient with distant metastasis, prior chemotherapy, or radiotherapy to the head and neck region and verrucous carcinoma or carcinoma in situ were excluded. The primary objective was to determine the prognostic significance of lymph node ratio in the survival rate — Overall survival and Disease free survival of patients. The secondary objective was to assess whether a risk stratification with a lymph node ratio is possible.

Patients were subjected to standard wide excision with or without reconstruction under frozen control and a comprehensive neck dissection. Meticulous examination of the lymph nodes was done by a single skilled head and neck pathologist. Minimum number of lymph nodes for a neck dissection was kept at 15 to avoid wide variations. Only pathologically node positive patients were included in the study and the lymph node ratio was calculated. Other nodal factors such as extra capsular spread, perineural infiltration, lympho–vascular emboli and tumour factors like margin adequacy, dysplasia at margins, depth of invasion and pattern of invasion were documented.

Postoperative radiotherapy was given according to our institution protocol for patients with high risk factors such as one or more positive lymph nodes, T3 & T 4 tumours, presence of adverse features like peri neural invasion, lympho vascular emboli or depth> 7 mm in combination, if other high risk factors are not present. Radiotherapy was scheduled within 4 to 6 weeks after surgery and administered using a 6 MeV Linear Accelerator. Total dose to the involved site was 60–66 Gy and uninvolved areas was 50 Gy. Chemotherapy was added along with radiotherapy if the nodes showed extra capsular spread or primary tumour excision showed positive margins. It consisted of 2 – 3 cycles of cisplatin 80– 100 mg/m².

Patients were followed up with focused history and physical examination – monthly for the first six months, 2x monthly up to two years. Any suspicion of recurrence in the primary site or the neck in clinical examination was confirmed with an incision biopsy or an ultra sound guided FNAC respectively and was managed accordingly i.e. nodal recurrence in the ipsilateral or contralateral side were surgically salvaged if operable and re-wide excisions were done for patients with operable recurrences at the primary site.

Overall survival (OS) and disease free survival (DFS) were calculated using the Kaplan Meier method. Cox proportional hazard model used for the univariate and multi variate analysis. A p value of less than 0.05 was considered statistically significant.

**Results**

**Patient demographics**

A total of 295 cases of primary squamous cell Carcinoma of tongue were operated at our institute in the stipulated period. Out of these patients, 51 patients were taken up for the study according to the criteria specified. Of these, 39 (78.6 %) were male. The majority (53 %) had N2 disease; the remainder had N1.

The mean number of nodes assessed was 23.16 and median was 23.0. Average nodal positivity was 1.98, with a mean nodal ratio of 9.04 % and a median nodal ratio of 7.1%. Range of follow–up of patients was 24 months to 36 months. Loco regional recurrences were 9. Local recurrences in tongue were 4. Ipsilateral nodal recurrences were 2, Contra lateral nodal recurrences were 4. Two patients have a simultaneous recurrence in the tongue and distant metastasis. One patient had a contra lateral neck node and a distant metastasis. Two patients have ipsilateral neck node and distant metastasis.

Distant metastasis occurred in 7 patients. Most common distant site metastasis was lung. Ten patients were dead due to the disease, 3 patients were dead due to other causes, and one patient was alive with disease. 49(96.1%) patients completed postoperative adjuvant radiotherapy, one patient did not complete the specified radiotherapy schedule and one patient took radiotherapy from outside and 15 patients received chemotherapy. Patient demographics are summarized in Table 1.
Overall Survival and Disease free survival

In the entire cohort of patients, 2 year overall survival was 70.3 % with a standard error of 7.3(Fig 1). The 2 yr disease free survival was 74.1 % with a standard error of 6.5 (Fig. 2). T classification, N classification, depth of invasion, absolute number of positive nodes, and extra capsular spread were associated with overall and disease free survival but did not approach statistical significance.

In univariate analysis, nodal ratio was significantly correlated with overall survival (p value=0.019) and there was a trend towards a positive correlation in disease free survival but it did not approach statistical significance.

In multivariate analysis only nodal ratio remained a significant predictor of overall survival (p value=0.024 and HR=6.268). Disease stage and extra capsular extension of regional disease all lose significance when compared with each other and with nodal ratio.

Table 1. Demographic distribution of the patient population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>21.4</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>78.6</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>14</td>
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<td>T2</td>
<td>29</td>
<td>50.9</td>
</tr>
<tr>
<td>T3</td>
<td>6</td>
<td>11.7</td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>3.9</td>
</tr>
<tr>
<td>N classification</td>
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<td></td>
</tr>
<tr>
<td>N1</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>N2</td>
<td>27</td>
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<td>Perineural spread</td>
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<td>41.2</td>
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<tr>
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<td>54.9</td>
</tr>
<tr>
<td>Not known</td>
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<td>3.9</td>
</tr>
<tr>
<td>Extra capsular spread</td>
<td></td>
<td></td>
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<td>52.7</td>
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<td>43.1</td>
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<tr>
<td>Lympho vascular spread</td>
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<td></td>
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<td>46</td>
<td>90.2</td>
</tr>
<tr>
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<td>3</td>
<td>5.9</td>
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<tr>
<td>Not known</td>
<td>2</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Lymph Nodal ratio

Given this significant association between nodal ratio and overall survival, the cut–off point was taken arbitrarily and compared with reference to the available literature. Three groups were taken: Lymph nodal ratio = 0–5, 6–10 and >10.Number of patients in 0–5 group were 19, 6–10 were 19 and more than 10 were 13. Patients with a LNR less than 5% fared the best (88.2% 2–year OS), followed by patients with LNR between 6% and 10% (74.1% 2–year OS), patients with a LNR of more than 10% fared the worst (37.8% 2–year OS) with a p value of 0.0187. Similarly LNR of 0–5 had a 83.6 % 2 yr DFS, 6–10 had a 82.9 % 2 yr DFS and > 10 had a 46.3 % DFS, showing a trend towards worse DFS though it was not statistically significant. Figure 3 and 4 demonstrate the Kaplan Meier curves for the respective LNR.

Discussion

Pathological nodal positivity is a principle prognostic factor in assessing survival in patients with tongue cancer and also a major deciding factor tailoring further adjuvant treatment1–5. But the prognostic implication may be limited by the extent of the regional dissection.
undertaken and extent of scrutiny by the pathologist. This stands to reason that with a higher number of nodes assessed, there is a lower risk that nodal metastases are missed. There is increasing recognition of the importance of a minimal acceptable number of lymph nodes retrieved and examined in other solid cancer sites, but there is little literature in the head and neck cancers to make recommendations for such a standard at present 10, 16, 17.

Moreover it is difficult to differentiate between the extent of surgical dissection and the extent of pathologic review of that dissection. A comprehensive neck dissection is not just a function of the extent of surgery performed but also the extent to which the specimen is subjected to pathologic examination. What is more important is that, if the metastatic node(s) is missed by a sub optimal neck dissection or a cursory review by the pathologist, it can result to avoidance of the adjuvant treatment for the patient. For example, there is a definite difference in the significance of a single lymph node identified in a neck dissection specimen containing 10 lymph nodes and a single lymph node identified in 20 lymph nodes. Hence lymph node ratio might be a better indicator.

Similar studies in Literature 6,18,19,20 that are available are retrospective in nature and they have taken up the Lymph nodal ratio in oral cancer which includes all the sub sites as a whole and have arrived at the significant association between lymph nodal ratio and survival.

In our study the minimum number of nodes dissected were kept to a standard of 15 nodes and above and the examination of the lymph nodes were done by a single dedicated head and neck pathologist. To the best of our knowledge there are no prospective studies available at present which has standardized the number of nodes harvested and also the examination of the lymph nodes by a single skilled pathologist, to reduce the bias further.

N3 patients were specifically excluded from this study because it is difficult to determine whether a nodal metastasis of greater than 6 cm is a single metastasis or multiple, matted metastases. Bilateral neck dissections were also excluded as the nodal ratio would be affected. We found that when the nodal ratio increases, survival decreases; this is most marked as nodal ratio crosses 2 cut-offs: low—risk patients have a nodal ratio of 5% or less. Moderate risk lies between 5% and 10%; patients with a nodal ratio higher than 10% fared the worst. There is a dramatic survival disadvantage, in fact, to being in the high—risk nodal—ratio group: 2—year overall survival in these patients is 37.8 %.

Because this is an indirect test, at best, and because nodal ratio inherently contains more information than overall number of positive nodes, it remains a strong predictor. However, as already mentioned, studies from other solid tumour sites have shown that absolute nodal count and nodal ratio are independent prognostic predictors of survival on multivariate analysis10–17.

The disadvantage of our study being is the short follow—up period whereas a longer follow—up might reveal more significant factors associated.

Specifically, it bears asking whether nodal ratio itself can now be used in therapeutic decision making. Is the presence of an elevated nodal ratio, for example, an indication for the addition of adjuvant therapy in the...
Significance of metastatic lymph node ratio in tongue cancer, V.M Bharath, et. al.

absence of other indications? This question has to be taken up further and addressed with randomized trials.

In conclusion, patients with squamous cell carcinoma tongue, the lymph nodal ratio, is a strong predictor of overall survival, independent of tumour size and its characteristics, absolute number of nodal metastasis or its characteristics. Further follow up of these patients would enable exploration of this concept in prospective, multi institutional trials on the impact of nodal ratio in treatment decisions.

References


