Abstract

Background. The aim of this study was to determine the prognostic significance of lymph node ratio (LNR) in node positive oral tongue squamous cell carcinoma (OTSCC).

Methods. In patients with pathological node positive OTSCC, the optimal cut-point for LNR was determined using the minimum p value method and the logrank test. The impact of this LNR cut-point on time to disease progression and overall survival was determined.

Results. In 72 patients with OTSCC, an LNR of 14.3% was found to have the greatest separation using the logrank test (p < .001).

LNR ≤14.3% predicted for longer time to disease progression (p < .001) and improved overall survival (p = .001). Patients with an LNR >14.3% experienced a higher rate of regional recurrence.

Conclusions. Our findings confirm the prognostic significance of LNR in patients with node positive OTSCC. Improving regional control in these high-risk patients may improve outcome.

Introduction

Oral tongue squamous cell carcinoma (OTSCC) are primarily managed surgically, with adjuvant treatment indicated to improve locoregional control and survival in patients considered at moderate to high risk of recurrence. An additional and emerging predictor for outcome of patients with oral cavity cancer is lymph node density (LNR). LNR is defined as the ratio of positive lymph nodes to the total number of lymph nodes removed. The aim of this study was to validate the prognostic significance of LNR in a cohort of node positive patients with OTSCC. The primary endpoint of the study examined the impact of LNR on time to disease progression. The secondary endpoint for analysis was overall survival.

Methods and Materials

At Westmead and Nepean Hospitals, Sydney, Australia, patients with biopsy confirmed OTSCC seen within the Multidisciplinary Head and Neck Cancer Service from 1980 onwards were registered on a computer database and data collected on patient demographics, surgery and radiotherapy details, tumor characteristics, and patient outcome.

Eligible patients underwent curative surgery as the primary treatment and had to have evidence of pathological nodal metastases. The LNR was calculated using the ratio of the number of positive lymph nodes reported to the total number of lymph nodes excised. The cut-point for optimal separation of LNR was obtained using the method described by Altman et al. The cut-point which minimized the p value obtained from the logrank test was used as the best separation of LNR into high and low risk categories. Measures of association of baseline variables to time to disease progression and overall survival were investigated using the proportional hazards regression model of Cox.

Prognostic variables included in the model were dichotomized and included sex, age (<40 vs ≥40 years), T stage (T1-T2 vs T3-T4), N stage (N0 vs N1-2), tumor differentiation (well differentiated vs not), tumor thickness (<4 mm vs ≥4 mm), positive margin status, perineural invasion, lymphovascular invasion, extracapsular extension, LNR at the optimal cut-point, and the addition of adjuvant radiotherapy with or without concurrent chemotherapy.

Results

Between 1980-2011, 287 patients underwent surgery for OTSCC including 192 patients who underwent a neck dissection. From this group, 72 were identified as having pathological nodal metastases and were analyzed.

The median follow-up was 55 months and median age at diagnosis was 60 years. The majority were male (67%) and aged 40 years or older (85%). Most had a T1-T2 primary cancer (75%), with 43 patients (60%) pathologically staged as N1. Fifty percent of tumors were graded as moderately differentiated. Tumor thickness was ≥4 mm in 82% of cases, and the majority (90%) were resected with negative margins. Thirty-three patients (46%) were noted to have evidence of extracapsular extension. Fifty-three patients underwent adjuvant radiotherapy (74%), and of these 5 patients also received chemotherapy given concurrently with radiation.

The mean number of excised lymph nodes was 22.8, with a mean LNR of 14.3%. Based on the minimum p method, an LNR of 14.3% was found to have the greatest separation using the logrank test (p < .001).

Fifty-four patients (75%) had an LNR ≤14.3%. Based on our analysis we have categorized LNR ≤14.3% as low-risk LNR and LNR >14.3% as high-risk LNR.

At the time of analysis, 33 patients have died; 21 as a result of OTSCC, with 1 patient dying as a result of a treatment-related complication. Disease recurrence occurred in 32 patients (44%) with the majority developing local or regional recurrence as the first site of recurrence (Table 1).

Table 1. First site of disease recurrence based on LNR.

<table>
<thead>
<tr>
<th>Site of recurrence</th>
<th>LNR≤14.3%</th>
<th>n</th>
<th>%</th>
<th>Site of recurrence</th>
<th>LNR&gt;14.3%</th>
<th>n</th>
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<td>100</td>
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</table>

Time to disease progression

In a univariate analysis, female sex, nodal stage N2-N3 and LNR >14.3% statistically significantly predicted for a shorter interval to disease progression.

On multivariate analysis LNR >14.3% was the only significant variable.

The median time to disease progression for patients with an LNR >14.3% was 9.4 months, compared to 73 months in patients with an LNR ≤14.3% (p < .001; hazard ratio (HR), 3.43; 95% confidence interval (CI), 1.76-6.70; Figure 1).

Overall survival

On univariate analysis, a significant improvement in overall survival was associated with a nodal stage of N1 (p = 0.003) and LNR ≤14.3% (p = .001).

Multivariate analysis demonstrated that only LNR >14.3% and age ≥40 years were significant predictors for worse overall survival.

The median overall survival for patients with an LNR >14.3% was 14.7 months, compared to 82.3 months with an LNR ≤14.3% (p = .001; HR, 3.28; 95% CI, 1.61-6.68; Figure 2).

Discussion

LNR has been postulated as a predictor of patient outcome, as LNR combines the variables of the number of positive nodes, reflecting the degree of tumor burden; as well as the total number of excised nodes which potentially acts as a surrogate for adequate dissection.

LNR studies of oral cavity cancer have utilized minimum p values, as well as median values to identify an LNR cut-off point for analysis, resulting in LNR thresholds ranging from 4.20% to 25%.

We included only node negative patients in our study, to minimise bias in determining an LNR threshold and found that an LNR >14.3% predicted for a poorer disease-free and overall survival.

Pathological nodal stage based on the TNM staging system, although a predictor for time to disease progression and overall survival on univariate analysis in our study, did not remain significant on multivariate analysis, suggesting that LNR may have greater prognostic significance than the traditional TNM nodal staging.

The majority of recurrences in patients with a high-risk LNR were regional (54% vs 37%), whereas in patients with a low-risk LNR, local recurrences predominated (47% vs 8%). These findings may explain, in part, the poorer survival rates in the higher risk group, as many will experience unsalvageable regional recurrence, and therefore support means to improve regional control in this group.

Conclusions

LNR is an independent prognostic predictor of outcome in patients with OTSCC. Our findings would suggest that an LNR >14.3% is associated with a worse outcome, and may be a more useful predictor than traditional nodal staging. Select patients with a high LNR may be considered for combined adjuvant treatment with the addition of chemotherapy to radiation, but optimally should be enrolled into a study to evaluate the benefit of more intensive treatment.

References


Contact

Prof Michael Veness
Department of Radiation Oncology
Crown Princess Mary Cancer Centre, Westmead Hospital
Westmead, NSW 2145, Australia
Email: michael.veness@health.nsw.gov.au
Phone: +61 2 9845 5200