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Lymph Node Ratio & Capsule Penetration as Independent Risk Factors In Oral Cavity Squamous Cell Carcinoma: An Institution Based Analysis

Yadav Dinesh[1*], Goyal Sumit[2], Yadav Ajay[3]

[1]Assistant Professor, Department of Surgical Oncology, MG Medical College Hospital and Research Centre, MGUMST, Jaipur, Rajasthan, India
[2]Assistant Professor, Department of Radiation Oncology, MG Medical College Hospital and Research Centre, MGUMST, Jaipur, Rajasthan, India
[3]Assistant Professor, Department of Medical Oncology, MG Medical College Hospital and Research Centre, MGUMST, Jaipur, Rajasthan, India

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***Corresponding author:** Dinesh Yadav

Abstract **Original Research Article**

Knowledge of independent prognostic factors in patients with oral caity squamous cell carcinoma is important for appropriate treatment decisions. Given the availability of aggressive therapeutic options with known side effects and burdens for the patient, choosing the correct treatment option is vital. Using a retrospective database of patients treated over a 1year period, independent prognostic factors for disease-free survival and overall survival were assessed. Univariate analysis was used to identify significant variables, and multivariate Cox regression analysis was used to determine independent prognostic factors. 200 patients with head and neck squamous cell carcinomas were analysed to identify prognostic factors for disease-free survival and overall survival. Although univariate analysis identified several significant factors, multivariate Cox regression analysis showed that capsule penetration and lymph node ratio were the only significant factors for disease-free survival and overall survival. Lymph node ratio is an independent predictor of survival and should be examined in every patient undergoing neck dissection.

Keywords: Oral cavity, Carcinoma, Capsule penetration, LNR.

INTRODUCTION

The LNR, was found to improve prognostic information in Ca breast, Ca Stomach, Colorectal ca & Melanoma [1-5]. The presence of cervical metastases has been consistently reported as a strong predictor of loco regional recurrence and poor survival in patients with squamous cell carcinomas of the head and neck [7].

In the current study, the prognostic role of LNR is analyzed in patients operated in SRCC. The cutoff point for the LNR in defining patients as high, medium & low risk groups identified. The importance of tumor stage in disease-free survival (DFS) and overall survival (OS) in patients with head and neck squamous cell carcinoma (SCC) is well known [6]. Tumour location, grade and histological aspects such as perineural invasion and capsule penetration have been associated with poorer DFS and OS. Nevertheless, some aspects of tumor biology and patient survival remain unclear. Given the availability of aggressive therapies and their known side effects, selection of patients who require aggressive treatment has become important.

In this study, we evaluated independent prognostic risk factors for DFS and OS in patients with SCC of the head and neck. We hypothesize that certain attributes lead to a poorer prognosis, whereas other attributes are unimportant.

MATERIALS AND METHODS

Study Design: We developed a retrospective patient database.

Study Sample

The study population was derived from patients who presented at the Shri Ram Cancer Centre (SRCC) for treatment of head and neck SCC between Oct. 2017 and Sept. 2018.

Inclusion Criteria

Included the diagnosis of SCC in the head and neck region and operative treatment at the primary

tumor site with/without adjuvant radiotherapy or radiochemotherapy.

Exclusion Criteria

Histological findings other than SCC, distant metastasis before neck dissection (ND) or were treated primarily outside SRCC.

Study Variables

Age and sex; tumor location, stage, size and grade; neck lymph node status; histological factors [blood vessel invasion (hemangiosis), lymph vessel invasion (lymphangiosis), capsule penetration, perineural invasion and conglomerate lymph nodes; resection margin; number of positive lymph nodes; lymph node ratio and adjuvant therapy (postoperative chemotherapy and/or adjuvant radiotherapy).

RESULT

Table-1: Descriptive statistics of 200 patients

Attribute		Number (%)
Sex	Male	187 (93.5)
Localization	BM	84(42)
	Lower alveolus	31(16.5)
	Upper alveolus	13(6.5)
	Tongue	40(20)
	FOM	4(2)
	RMT	18(9)
TNM stage	Stage I–II	66(33)
	Stage III–IV	134 (67)
Tumor stage	T1–2	111(55.5)
	T3–4	89 (44.5)
Lymph node status	N0	93(46.5)
	N1	22(11)
	N2a	9 (4.5)
	N2b	58 (29)
	N2c	18 (9)
Tumour Grade	Well Differentiated	98 (49)
	Moderately Differentiated	93 (46.5)
	Poorly/un-differentiated	9 (4.5)
Perineural invasion	No	178 (89)
	Yes	22 (11)
Lymphangiosis	No	173 (86.5)
	Yes	27 (13.5)
Hemangiosis	No	187 (93.5)
	Yes	13(6.5)
Capsule penetration	No	164 (82)
	Yes	36 (18)
Conglomerate lymph nodes	No	178 (89)
	Yes	22 (11)
Resection margin	Negative	196 (98)
	Positive	04(02)
No. of + nodes	0	84(42)
	1	40(20)
	2–5	58 (29)
	>5	18 (9)
Lymph node ratio	>50%	18(9)
	11%-50%	49 (24.5)
	5%-10%	45(22.5)
	<5%	88 (44)

In total, 200 patients were included. The mean age was 56 (range, 28–77) years. Most (93.5%) patients were men. Most patients had a tumor in the buccal mucosa (42%), followed by the tongue (20%), lower alveolus (16.5%), RMT (9%), upper alveolus (6.5%) and FOM (2%). Most patients presented with a stage III &IV tumor (67%), followed by stage I & II (33%). Regarding T-status, most patients presented with a T2 tumor (36%). Lymph node status was pN0 in 46.5% of patients, followed by pN2b in nearly 29% of patients.

Because patients with distant metastasis at diagnosis were excluded, all patients were in the M0 state.

Tumour grade was dominated by patients with well (49%) or moderately (43%) differentiated tumors. Only a few patients presented with poorly-differentiated or undifferentiated tumors. Perineural invasion was seen in 11% of patients; the percentage of lymphangiosis, hemangiosis, capsule penetration and conglomerate lymph nodes was 13.5%, 6.5%, 18% and 11%, respectively. Operative success, defined as a negative resection margin (R0 resection), was achieved in 98% of patients. R1 resection was achieved in 2%. Twenty eight (14%) patients underwent radical ND on the ipsilateral side. The largest proportion of patients was treated with modified radical ND (78.5%), followed by RND (14%) and selective supraomohyoidal (7.5). Given the small number of patients who underwent bilateral ND, only a minority (14%) of patients underwent more than five levels of ND.

Results of neck dissections demonstrated a pN0 situation in 42% of patients. One or 2–5 lymph nodes were positive in 20% and 29% of patients, respectively. In 9% of patients, more than five lymph nodes were affected. Nearly two thirds of patients had lymph node ratios (number of negative lymph nodes/ total number of excised lymph nodes) <10%. In total, 39(19.5%) patients received no adjuvant therapy, 136 (68%) patients received radiotherapy, 12.5% received combined radiochemotherapy.

Two-thirds of patients experienced no recurrence during follow-up. Recurrence was observed in 67 (33.5%) cases; distant metastasis occurred in 23 of these patients. In total, 107 (53.5%) patients were disease free after follow-up, 13.7% of patients suffered recurrence but survived follow-up, 19.9% of patients died after recurrence and 13.1% died of other causes. In total, 129 patients survived follow-up.

Univariate analysis identified the following factors as significantly affecting DFS: age, tumor location, stage, pT status, pN status, perineural invasion, lymphangiosis, hemangiosis, capsule penetration, conglomerate lymph nodes, resection margin, number of positive excised lymph nodes and lymph node ratio. The highest level of significance was found for capsule penetration and lymph node ratio ($p < 0.001$), followed by conglomerate lymph nodes, lymphangiosis and positive resection margin.

Univariate analysis identified the following factors as significantly affecting OS: age, tumor location, stage, pT status, pN status, perineural invasion, lymphangiosis, hemangiosis, capsule penetration, conglomerate lymph nodes, resection margin, number of positive excised lymph node, and lymph node ratio. OS also significantly differed according to the use of adjuvant radiotherapy. The highest level of significance was obtained for capsule penetration, conglomerate lymph nodes, pN status and lymph node ratio ($p < 0.001$), followed by overall staging.

Multivariate analysis revealed two independent predictor variables for DFS: lymph node ratio and capsule penetration. Lymph node ratio was divided into four groups: >50-100% (reference), >10–50%, >5-10 and <5%. The OR for a lymph node ratio of <10% was 1.698 ($p = 0.023$) and that for a ratio of <5% was 2.271 ($p < 0.001$). The OR for an event was 1.693-fold higher when capsule penetration was evident than when the capsule was intact ($p = 0.014$). Multivariate analysis for OS identified the same independent predictors as for DFS. The ORs for lymph node ratio were 2.269 and 2.904 for 5–10% and <5%, respectively, compared with the reference (100–50%). The OR for capsule penetration was 1.886 ($p = 0.009$).

DISCUSSION

In the data analysis of 200 patients with head and neck SCC, two variables were found to be independent prognostic factors in multivariate analyses: lymph node ratio and capsule penetration. The impact of capsule penetration on loco regional DFS and OS is well known. Even in patients with clinically negative necks, occult metastases with capsule penetration occur, putting the patient at high-risk of under treatment. This finding also disproves the former idea that extracapsular spread was associated with larger lymph node metastases and fixed lymph nodes [8].

In an investigation of 266 patients with SCC of the tongue, Myers *et al*., reported 5-year OS rates for patients with pathological node-negative necks, node-positive necks without extracapsular spread and node-positive necks with extracapsular spread of 75%, 50% and 30%, respectively [9]. Despite postoperative radiotherapy in 89% of patients with extracapsular spread, the regional failure rate was 29%. Thus, the authors concluded that further adjuvant therapy was necessary for regional and distant control and improved survival. Our data suggests the importance of extracapsular spread for DFS and OS. Of 36 patients with extracapsular spread who received no adjuvant therapy, 28(14%) died during follow-up. Adjuvant therapy significantly increased OS in patients with extracapsular spread to 50% (18/36 patients died during follow-up).

Perineural invasion, another histological aspect discussed as an independent prognostic factor, was not found to be significant in this multivariate analysis [8]. Previous reports have indicated that perineural invasion is a strong predictor for local and locoregional recurrence, and thus should be included in pathological examinations and treated with adjuvant therapy. In cutaneous cancer of the head and neck, perineural invasion is also a predictive factor for survival. In our

study, perineural invasion was identified as significant in univariate analyses (p = 0.031 for DFS and p = 0.034 for OS), but it was not an independent prognostic factor in multivariate analysis. These findings are important because most data supporting associations between perineural invasion and outcome have been derived from univariate analyses.

Lymph node ratio was the second independent prognostic factor. Previous studies have demonstrated that this variable is an important diagnostic tool in certain tumors, such as gastric, endometrial, colorectal and pancreatic cancers. To our knowledge, only few reports have investigated lymph node ratio as a prognostic tool in head and neck cancer.

Shrime *et al*., suggested that the ratio between the number of excised and that of positive lymph nodes was a predictive factor for outcome [10]. In an investigation of 386 patients with oral SCCs, Gil *et al.*, reached the same conclusion. Shrime *et al*., used two cut-off points (6%, 13%), whereas Gil *et al*., used only 6%. Both studies obtained similar results and demonstrated significant effects of lymph node ratio on DFS and OS.

Suslu *et al*., reached the same conclusion about the importance of lymph node ratio, using 4% as the cut-off value for a significant difference in outcome [11]. The present study used a method for calculating cut-off points (the 'maximally selected rank statistic' method) as described by Lausen and Schumacher10 and applied by Shrime *et al*., However, instead of defining lymph node ratio as positive lymph nodes/all excised lymph nodes, we used the percentage of negative lymph nodes/all excised lymph nodes.

This technique allowed us to include all patients with negative lymph node status. This method was used for two reasons. First, our lymph node status data demonstrated no significant difference between pN0 and pN1 status. In particular, patients who underwent extensive ND and excision of a large number of lymph nodes had good prognostic outcomes if only one lymph node was positive. DFS and OS in these patients were similar to those in patients with a negative neck. In contrast, the recurrence rate was high in patients who underwent selective ND procedures, especially those who were thought to have negative neck status. Another reason for our calculation of negative instead of positive lymph nodes was the likelihood that 'the next excised lymph node' would also be negative; thus, this type of calculation is more accurate.

Ebrahimi *et al.*, also described the importance of adequate ND, demonstrating that nodal yield was an independent prognostic factor in patients with oral SCC undergoing elective ND [12]. The combined use of nodal yield and lymph node ratio should inform the surgeon about the risk of encountering additional positive lymph nodes and may be a useful prognostic tool in the treatment of head and neck SCC.

CONCLUSION

According to AJCC extracapsular spread is defined as high risk factor that classify patient for adjuvant Chemoradiotherapy. In our study lymph node ratio also classified as high risk factor for DFS and OS on multivariate analysis. It needs larger patient database to include LNR to AJCC staging.

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