ORIGINAL ARTICLE

HISTOPATHOLOGICAL PREDICTORS OF NODAL METASTASES IN ORAL SQUAMOUS CELL CARCINOMA

Sana Mirza[1], Naila Irum Hadi[2], Saima Akram[1], Noor-ul-Wahab[3], Zohaib Akram[4].

[1]. Department of Oral Pathology, Ziauddin College of Dentistry, Ziauddin University and Hospitals, Karachi Pakistan

[2]. Department of Pathology, Ziauddin Medical College, Ziauddin University and Hospitals, Karachi Pakistan

[3]. Department of Maxillofacial Surgery, Ziauddin College of Dentistry, Ziauddin University and Hospitals, Karachi Pakistan

[4]. Department of Periodontology, Ziauddin College of Dentistry, Ziauddin University and Hospitals, Karachi Pakistan

ABSTRACT

Background: Oral cancer is regarded as the sixth most common malignant tumor and is one of the leading cause of death. Lymph node metastasis is a major factor for the prognosis of oral squamous cell carcinoma (OSCC). The objective of study was to compare the lymph node metastases with different histopathological parameters to identify high risk patients with the need for extensive treatment plans.

Methods: 140 histologically proven OSCC patients visiting Ziauddin College of Dentistry were included in this study. The clinico-pathological parameters were compared by using Chi-square, Kruskal-Willis and Mann-Whitney.

Results: There were 90 male and 50 female patients with 29.8% in 49-58 years age group. Buccal mucosa was the most common site of tumor. The predominant morphology of OSCC was moderately differentiated OSCC with stage IV disease. Lymph node metastasis was present in 48.6% of patients. Perineural invasion (22.9%), lymphovascular invasion (8.6%) and distant metastasis (11.1%) were also recorded. The mean tumor size was 3.45mm ± 1.95mm and mean tumor thickness was 1.8 ± 1.6mm.

Conclusion: A significant association between grade, stage, tumor size, tumor thickness and distant metastasis with lymph node involvement was found. However further studies with larger sample size are required to validate these results.

KEY WORDS: Oral squamous cell carcinoma; Lymph node metastases; Tumor size; tumor thickness.

INTRODUCTION

Oral cancer is regarded as the sixth communal malignancy and is the foremost cause for the death [1]. Pakistan and India fall in high risk zone of oral squamous cell carcinoma (OSCC) with prevalence rates of 10% and 40% respectively, as presentation is late and treatment is not optimum. Regardless of recent advancements in surgical and adjuvant chemo-radiotherapy the five-year survival rate remains to be 50% [2].

The lymph node involvement reflects biological aggressiveness of OSCC. As the oral cavity have abundant lymphatic network, the risk of development of nodal metastasis varies between 19%-57% even in the early stages [2]. This causes the survival rate to be decreased up to 50% or more[4]. Currently the size and thickness of tumor are used to predict the prognosis of oral cancer[5]. Increased tumor size and thickness are related to the lymph node metastases, recurrence of tumor as well as poor prognosis[6]. There is 12% risk of metastasis when tumor thickness is of 6 mm or less; however when thickness was 7 mm or more, the risk increased to 57% [7]. The outcome of OSCC is greatly influenced by the stage of the disease as well. Early staged tumors have better prognosis and less aggressive treatments [8].The objective of this study was to compare lymph node metastases with different histopathological parameters in order to identify the high risk patients for extensive treatment and to predict their prognosis.

METHODS

This cross-sectional study comprises of 140 OSCC patients aged 18–80 years with no sex predilection,

Corresponding Author: Sana Mirza*

visiting the Department of Maxillofacial Surgery, Ziauddin College of Dentistry, between April 2014 to July 2015. The study approval was taken by the Ethics Review Committee, of Ziauddin University (0241114SMMPHIL). Eligible participants were informed and written consent was sought.

Oral specimens were fixed overnight in 10% buffered formalin and routinely processed. 4-5 µm thick, paraffin embedded tumor sections were stained with Haematoxylin and Eosin. Histological grade was assessed according to Broders classification [10]. Stage was determined by using American Joint Committee on Cancer (AJCC) TNM classification[11].

SPSS (v.21.0) was used for statistical analysis. Data for categorical variables were expressed in frequencies and percentages. Chi-square test was used to find the association among different groups. Kruskal-Willis and Mann-Whitney test were used to find the difference in the mean ranks of tumor size and thickness. P-value less than 0.05 was regarded as statistically significant.

RESULTS

There were 90 (64.3%) male and 50 (35.7%) female OSCC patients. 29.8% patients were in 49-58 years age group. Lymph node metastases were present in 72 (51.4%) OSCC patients with, 22 (15.7%) N1a, 11 (7.8%) N1b, 10 (7.1%) N2a, and 29 (20.7%) N2b. Both gender and age had no significant association with cervical lymph node metastasis.

Buccal mucosa was found to be the most common site of tumor (69; 49.3%) showing no significant association with lymph node metastases (p<0.268). 87(62.1%) of cases were moderately differentiated (p<0.026) while 71(50.4%) patients were Stage IV disease (p<0.05).

Table 1 Association of lymph node involvement with tumor stage and grade

Lymph nodes	Stage n (%)				Grade n (%)		
	I	II	III	IV	G1	G2	G3
N()	10 (14.7)	35 (50.0)	15 (22.1)	9 (13.2)	13 (19.1)	47 (69.1)	8 (11.8)
N1a	—	—	7 (31.8)	15 (68.2)	4 (18.2)	13 (59.1)	5 (22.7)
N1b	—	1 (9.1)	2 (18.2)	8 (72.7)	1 (9.1)	5 (45.5)	5 (45.5)
N2a	—	—	—	10 (100.0)	2 (20.0)	8 (80.0)	—
N2b	—	—	—	29 (100.0)	3 (10.3)	14 (48.3)	12 (41.4)
Total	10 (14.7)	35 (25.0)	24 (17.1)	71 (50.7)	23 (16.4)	87 (62.1)	30 (21.4)
p-value	0.00†*				0.02†*		

† Obtained from Pearson Chi-Square test.*Significant at <0.05. (N - Lymph Node Involvement)

Perineural invasion was present in 32 patients (p>0.05) while LVI invasion in 12 patients (p<0.074).The mean tumor size was 3.45mm ± 1.95mm and showed statistically significant association with lymph node metastases (p<0.032). Mean tumor thickness was 1.8 ± 1.6mm) and showed statistically significant association with lymph node involvement (p<0.05)

Table 2: Association of lymph nodes with invasions, tumor size and thickness

Lymph nodes	Perinerual invasion n(%)		Lymphovascular invasion n(%)		Distant invasion n(%)		Tumor size (mm)	Tumor Thickness (mm)
	Absent	Present	Absent	Present	Absent	Present		
No	49 (72.1)	19 (27.9)	66(97.1)	2(2.9)	68 (100.0)	_	3.15±1.25	1.44±1.3
N1a	17 (77.3)	5(22.7)	17(77.3)	5(22.7)	19 (86.4)	3(13.6)	2.73±1.36	2.12±0.66
N1b	10 (90.9)	1(9.1)	10(90.9)	1(9.1)	11 (100.0)	_	4.63±2.66	2.05±1.19
N2a	9(90.9)	1(10.0)	9(90.9)	1(10.0)	10 (100.0)	_	3.15±1.25	1.44±1.3
N2b	23 (79.3)	6(20.7)	26(89.7)	3(10.3)	24 (82.8)	5(17.2)	3.15±1.25	1.44±1.3
Total	108 (77.1)	32(22.9)	128 (91.4)	12(8.6)	132 (94.3)	8(5.7)	Mean= 3.45±1.95	Mean=1.8±1.6
p-value	0.52†		0.07†		0.004†*		0.032*	0.000*

† Obtained from Pearson Chi-Square test. *Significant at <0.05 (N - Lymph Node Involvement)

DISCUSSION

In line with the reported evidence, Lymph node metastases is found in approximately 34%-50% of OSCC patients [12]. We report an increased incidence of OSCC in older aged males. However, the incidence is increasing in younger age group patients as well as in females[13] due to increased usage of tobacco, alcohol and dietary inadequacies like insufficient intake of vegetables and fruits[14].

In our study, buccal mucosa (46.8%) was the commonly involved site. However, in the west, tongue along with floor of mouth are commonest sites of OSCC 4 due to practices of alcohol use. [13]

Tumor size and thickness showed significant association with lymph nodes metastasis (p<0.032) (p<0.05) which is in agreement with other studies [15,16,17]. However, disparity exists for optimal tumor thickness cutoff point [18, 19]. In our study the cut off for tumor thickness is 3.1 mm while earlier studies have proposed 3mm to 6mm as cutoff point[18]. The prognosis changed significantly at a cut–off of less than 4mm of tumor thickness with local control, nodal disease and survival rates of 91%, 8%, and 100% respectively, compared with 84%, 48% and 74% for those 4mm or more[20]. So, Early detection of tumor will result in smaller tumor size, tumor thickness< 3 mm and hence better prognosis, quality of life and long term survival.

Concurrent with other studies[21, 22], we reported significant association of tumor stage with lymph node metastasis (p<0.05).It has been suggested to combine TT with the pathological staging to obtain a modified pT classification[23] as TT being third dimension of tumor is accurate prognosticator of metastasis[22]. In our study, majority of cases were moderately differentiated showing significant association with lymph node metastasis [6, 10]. Furthermore, grading system is considered as poor indicator of outcome and response it is attributed to intra-observer variability in morphological assessment of degree of keratinization, pleomorphism (cellular + nuclear) and mitosis [24].

Lymphovascular and PNI are reported to have a substantial association with tumor size, grade, nodes and with overall prognosis[25], while others found no significant association of these variables[26,27].Our study showed no significant association with PNI. The variation in significance of PNI is most likely attributed to inconsistency in the methodology along with limited number of cases being analyzed [28]. Therefore, for validation advance studies are required.

CONCLUSION

A significant association between nodal involvement and grade, stage, tumor size and tumor thickness was found in oral squamous cell carcinoma. We recommend incorporation of these histopathological variables not only in protocols for treatment but also for assessment of prognosis. However further studies with larger sample size are warranted to justify these results.

ACKNOWLEDGEMENTS

We are thankful to Ziauddin University for providing research grant for this project. (ZU/HR/15/80420/02). We are also grateful to Dr Fouzia Lateef, Dr Adnan Zuberi, Dr Uzma Bukhari and the staff at Department of Histopathology Ziauddin Hospital North for their valuable insight and technical assistance.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136: 359-386.
2. Markopoulos AK. Current aspects of oral squamous cell carcinoma. Open Dent J. 2012;6:126-130
3. Jang WI, Wu HG, Park CI, Kim KH, Sung MW, Kim MJ et.al; Treatment of patients with clinically lymph node-negative squamous cell carcinoma of the oral cavity. Jpn J Clin Oncol.2008; 38(6): 395-401
4. Alkaisi A, Zaidan H, Al Kabtan I. The predictive value of tumor depth for cervical lymph node metastasis in oral squamous cell carcinoma; prospective and retrospective study in Iraq. J Cancer Sci Ther. 2014; 6: 253-257.
5. Garzino-Demo P, Dell'Acqua A, Dalmasso P, Fasolis M, Maggiore GM, Ramieri G, Berrone S, Rampino M, Schena M. Clinicopathological parameters and outcome of 245 patients operated for oral squamous cell carcinoma. J Craniomaxillofac Surg. 2006;34(6):344-350.
6. Jerjes W, Upile T, Petrie A, Riskalla A, Hamdoon Z, Vourvachis M et.al; Clinicopathological parameters, recurrence, locoregional and distant metastasis in 115 T1-T2 oral squamous cell carcinoma patients. Head Neck Oncol. 2010;2:1-40
7. Lodder WL, Teertstra HJ, Tan B, Pameijer FA, Smeele LE, van Velthuysen ML, van den Brekel MW. Tumour thickness in oral cancer using an intra-oral ultrasound probe. Eur Radiol. 2011;21(1):98-106.
8. Van der Schroeff MP, de Jong RJB. Staging and prognosis in head and neck cancer. Oral Oncol. 2009;45(4):356-360.
9. Dancey JE. Assessing benefit in trials: Are we making progress in assessing progression in cancer clinical trials? Cancer. 2015;121(11):1728-1730.
10. Akinyamoju AO, Adeyemi BF, Kolude B, Adisa AO. Histological grading of oral squamous cell carcinoma patients in Ibadan using Bryne's and Broders' grading systems--a comparative study. Afr J Med Med Sci. 2013;42(4):333-337.
11. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-1474.
12. Tankéré F, Camproux A, Barry B, Guedon C, Depondt J, Gehanno P. Prognostic value of lymph node involvement in oral cancers: a study of 137 cases. Laryngoscope. 2000; 110: 2061-2065.
13. Hernández Guerrero JC, Jacinto Alemán LF, Jiménez Farfán Farfán MD, Macario Hernández A, Hernández Flores F, Alcántara Vázquez A. Prevalence trends of oral squamous cell carcinoma. Mexico City's General Hospital experience. Medicina Oral, Patologia Oral y cirugia bucal.2013; 18: 306-311.
14. Mackenzie J, Ah-See K, Thakker N, Sloan P, Maran AG, Birch J et.al; Increasing incidence of oral cancer amongst young persons: what is the aetiology? Oral Oncol. 2000; 36: 387-389.
15. Koo BS, Lim YC, Lee JS, Choi EC. Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head Neck. 2006; 28: 896-901.
16. Olzowy B, Tsalemchuk Y, Schotten KJ, Reichel O, Harréus U. Frequency of bilateral cervical metastases in oropharyngeal squamous cell carcinoma: a retrospective analysis of 352 cases after bilateral neck dissection. Head Neck. 2011; 33: 239-243.
17. Aslam F, Atique M, Aslam M, Sarfraz T, Ayaz B, Alamgir W. Relation of tumour thickness with lymph node metastasis in oral squamous cell carcinoma.Pafmj .2012;64(4):529-533.
18. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity. Cancer. 2009; 115: 1489-1497.
19. Veness MJ, Morgan GJ, Sathiyaseelan Y, Gebski V. Anterior tongue cancer and the incidence of cervical lymph node metastases with increasing tumour thickness: should elective treatment to the neck be standard practice in all patients? ANZ J Surg. 2005; 75: 101-105.
20. Kane S, Gupta M, Kakade A, D'Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. Eur J Surg Oncol. 2006; 32: 795-803
21. Shingaki S, Takada M, Sasai K, Bibi R, Kobayashi T, Nomura T et.al; Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. Am J Surg. 2003; 185: 278-284.
22. Sobin L, Wittekind C. International Union Against Cancer (UICC): TNM classification of malignant tumors 6th edition. 2002. New York: Willey–Liss.
23. Greenberg JS, El Naggar AK, Mo V, Roberts D, Myers JN. Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Cancer. 2003; 98:508-515.
24. Bier-Laning CM, Durazo-Arvizu R, Muzaffar K, Petruzzelli GJ. Primary tumor thickness as a risk factor for contralateral cervical metastases in T1/T2 oral tongue squamous cell carcinoma. Laryngoscope.2009; 119: 883-888.
25. Capote-Moreno A, Naval L, Muñoz-Guerra MF, Sastre J, Rodríguez-Campo FJ. Prognostic factors influencing contralateral neck lymph node metastases in oral and oropharyngeal carcinoma. J Oral Maxillofac Surg.2010; 68: 268-75.
26. Wallwork BD, Anderson SR, Coman WB. Squamous cell carcinoma of the floor of the mouth: tumour thickness and the rate of cervical metastasis. ANZ J Surg. 2007; 77: 761-764.
27. Weijers M, Snow GB, Bezemer DP, Van der Wal JE,

Van Der Waal I. The status of the deep surgical margins in tongue and floor of mouth squamous cell carcinoma and risk of local recurrence; an analysis of 68 patients. Int J Oral Maxillofac Surg. 2004; 33: 146-149.

28. Binmadi NO, Basile JR. Perineural invasion in oral squamous cell carcinoma: a discussion of significance and review of the literature. Oral Oncol. 2011; 47: 1005-1010.