Comparative study of various grading systems & depth of invasion in oral squamous cell carcinoma and their value in predicting cervical lymph node metastasis

[1]Takvani Mili D., MDS, Dental Surgeon at Takvani Dental & Children Hospital, Jamnagar, Gujarat, India.

[2]Phulari Rashmi G S, MDS ,Professor, Department of Oral Pathology & Microbiology, Manubhai Patel Dental College & Hospital, Vadodara, India.

[3]Shah Arpan K, MDS, Reader, Department of Oral Pathology & Microbiology, Manubhai Patel Dental College & Hospital, Vadodara, India

Corresponding Author: Takvani Mili D., MDS, Dental Surgeon at Takvani Dental & Children Hospital, Jamnagar, Gujarat, India.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Oral squamous cell carcinoma invades the surrounding tissue and metastasize to cervical lymph nodes. Their highly variable prognosis makes the treatment of the neck controversial in patients with a clinically negative neck or with early-stage oral cavity carcinoma. In such cases having a certain pathological variable to depend upon for deciding the course of neck dissection can have a deeper impact on the quality of patients life post the treatment by preventing unnecessary surgical removal of the tissues.

Aim: To compare various grading systems & depth of invasion in oral squamous cell carcinoma and their value in predicting cervical lymph node metastasis.

Materials & Methods: We retrospectively analyzed different histopathological variables, depth of invasion & compared various grading systems in OSCC & their value in predicting cervical LN metastasis in 60 cases of OSCC.

Results: Bryne's grading system and tumor Depth Of Invasion showed the most significant association with occurrence of metastasis. Statistical analysis showed, a cut off value of 9.5 mm when DOI was added to the total score of Bryne's grading system, the results were statistically significant with P Value:0.003, Sensitivity:83.3%, Specificity: 53.3% with positive predictive value : 64.1% and negative predictive value: 76.2% suggesting that the accuracy of the Bryne's grading system was improved for prediction of metastasis when DOI was added as an additional parameter.

Conclusion: Our study demonstrate the importance of tumor depth of invasion as independent prognostic factor

and its ability to strengthen grading system for prediction of metastasis in patients with OSCC.

Keywords: OSCC, Cervical, Lymph

Introduction

Squamous cell carcinomas of the oral cavity are among the ten most common cancers in the world, accounting for approximately 3-5% of all malignancies (Weir et al, 1987).[1]Lymph node metastasis occur in about 40% of patients with oral cancer.[1,2]According to the published data, the incidence of occult metastases to the neck can range from 15% to 60% depending on different prognostic factors.[2] Occult means the metastases are hidden or not easily seen.

Cervical lymph node metastasis is the single most important prognostic factor for patients with head and neck carcinoma. Therefore, appropriate management of the neck is important. There is great controversy regarding the optimal therapy for clinically negative necks. Given the rate at which occult metastasis from oral cavity cancer encountered is of 34%, it is argued that nearly two thirds of the patients would be exposed to the morbidity of a neck dissection unnecessarily. There are still many doubts concerning the best way to approach neck disease in the case of early-stage lesions (T1 and T2).

Of the different variables that are related to neck metastasis including multiple factorial grading systems, two of the most important are depth of invasion and tumour thickness. These two terms are sometimes used interchangeably, but their meanings are not the same. Depth of invasion is used to define the extension of tumour beneath the epithelial surface, where epithelium is destroyed. Tumour thickness is used to define the measurement of a tumour's vertical bulk; it encompasses both the exophytic and endophytic portions of the tumor.[4,5]

Our study re-examined the tumour depth of invasion parameter as a single parameter in the primary tumour that correlates with evidence of regional lymph node metastasis and as an additional parameter in grading system.

Materials and methods

This was a longitudinal historical cohort studyinvolving cases of Oral Squamous Cell Carcinoma resection with concomitant neck dissections, comprising of 30 cases positive for lymph node metastasis and 30 cases negative for lymph node metastasis were retrieved from the archives of the Department Of Oral Pathology And Microbiology, MPDC, Vadodara andGoraj cancer institute. Inclusion criteria for cases were set as Histopathologically diagnosed cases of Oral Squamous Cell Carcinoma which had undergone surgical excision of the tumour along with concomitant neck dissections. Three sections of 4micron thickness were made using soft tissue microtome and they were stained with H & E stain. The slides were assigned reference numbers, and hence the clinical details and lymph node status of the patients were masked for the examiners.Grading wasdone according to the grading systems:

1. Broder's (1920) classification
2. Jakobbson et al (1973) histologic grading system
3. Anneroth et al (1987) histologic grading system
4. Bryne's (1989, 1992) (ITF) Invasive Tumor Front Grading System

Depth of invasion: Microscopic tumour depth was taken as the infiltrative portion of the tumour which extended below the epithelial surface of the adjacent mucosa. Where the epithelium was destroyed, it was measured after reconstructing a virtual surface. The deepest extent of the tumour was marked using a marker pen under the 4x objective. A perpendicular was drawn on the surface line from the deepest point and this distance was then

measured, in millimetres, below the reconstructed line [as shown in Fig. 2], on a scale with a least count of 1 mm.

Results

Grading system: Out of four systems compared a significant relationbetween Bryne's grading system and regional metastasis (P value 0.032 , Odds aRatio 1.284, 95% C.I. (1.013,1.627) showing over all 58.3% correct classification.

Depth of Invasion : Graph 1

Stepwise multivariate logistic regression analysis for Depth Of Invasion showed significant association between the microscopic depth of invasion P value < 0.001 95% CI (0.679 , 0.907), sensitivity 76.7%,specificity 70% , positive predictive value 71.9% was found with the occurrence of metastasis.

Relationship of tumour depth with nodal metastasis, taking 7.1 mm as a cutoff value:

A cut-off value of 7.1mm for tumour depth was given after the statistical analysis was done. Taking a cut-off at 7.1 mm, of the 32 cases where depth of invasion value was more than 7.1mm, 23 cases were positive for regional metastasis and of 28 cases showing depth of invasion value below 7.1mm, 7 cases were positive for regional metastasis. The sensitivity was 76.7% and specificity was 70.0%. Positive predictive value was 71.9% (Table 2)

Combination of Bryne's grading system with DOI:

With the help of statistical analysis, a cut off value of 9.5 mm was obtained when DOI was added to the total score of Bryne's grading system, the results were statistically significant with P Value:0.003, Sensitivity:83.3%, Specificity: 53.3% with positive predictive value : 64.1% and negative predictive value: 76.2%.

This suggested that the accuracy of the Bryne's grading system was improved for prediction of metastasis when Depth OfInvasion was added as an additional parameter.

Discussion

In patients with a clinically negative neck or with early-stage oral cavity carcinoma (T1/T2, N0)the treatmenthas always been controversial. The two options for managing the neck in these cases are elective neck dissection and a wait-and-see approach.When the risk of cervical lymphnode involvement is greater than 15%- 20%Elective Neck Dissection is recommended. Being both diagnostic and therapeutic, it provides pathological information on the status of neck nodes, thus helping to determine the need for adjuvant therapies.It removes any clinically undetectable metastases, however; a significant number of patients undergone will have no evidence of regional lymph node metastases and may be subjected to the potential morbidity of a neck dissection.[3,5]

Since cervical lymphnode status is the most important prognostic factor in patients with head and neck carcinoma, prediction of nodal metastasis becomes important factor and identifying a reliable parameters that predict the risk of cervical lymphnode involvement is of great value.[6,7]

Many studies have demonstrated that depth of invasion can be a factor which can be a reliable factor for predictions of cervical metastasis in oral squamous cell carcinoma. Other studies have shown that there is a statistically significant association between depth of invasion and neck node metastasis in all patient groups, including clinically N0 groups.[4,5,9,10]

In articles concerning oral carcinoma, maximum tumour thickness was most often evaluated with an optical micrometer with various measurement techniques, depending on whether the mucosal surface, the tumour surface, or the ulcer base was chosen as the starting point.[4,5]

Some authors adopted the technique developed by Breslow and measured vertically starting from the tumour surface or the base of the ulcer base (Figure 1 A–D). In those cases in which the tumour was exophytic, the most perpendicular section was measured from the tip of the papilla to the maximal depth. Alternately, an imaginary line indicating the level of the adjacent intact mucosa (Figure 1 B–E) or of the basal membrane(Figure 1 C–F) can be considered the starting point for measuring the thickness of the tumour into the underlying tissue to the deepest pointof invasion. Moore et al[9] used the technique proposed by Breslow, as well as a second measurement obtained from an imaginary ''normal mucosal line'' for comparison. They found that longer survival of most patients with verrucous cancer correlated better with thickness as measured from the line of a ''basement membrane constructed through the tumour'' than with the entire thickness of the exophytic tumour. Woogar et al[10] considered thickness as the entire tumour measurement and depth as the amount from the surrounding normal mucosa.[4,5]

In current study, "Depth of invasion",as a parameter, was re-examined and its value in predicting lymph node metastasis. We also analysed reliability of four widely used grading systems.

In current study we also analysed the cutoff point, which was found to be strongly associated with neck metastasis when tumour depth categorized greater than 7.1 mm, in conversion N0-N1 group, tumour depth exceeding 7.1 mm was noted in 23 out of 32 patients with positive predictive value 71.9% in occurrence of metastasis.

Similar studies were done byShaha*et al*[5], Alkaisi A *et al*[6]and Hosal*et al*[7]found the tumour depth cut off value between less than 9mm,4mm and 2mm to 9mm, respectively.

In the literature, discussion remains as to which cut-off point is optimal, and in the more recent literature, cut-off points range between 3 and 8 mm. Pentenero*et al*showed that in the literature the cut-off thickness predicting neck metastasis and survival varied from 1.5 mm to 10mm. Thus, it remains difficult to choose a reliable cut-off point for elective neck treatment and/or adjuvant radiotherapy.[4,5,6]

Comparing the four widely used grading systems being mentioned in materials and methods our study results showed Bryne's invasive tumour front grading system having most significant relation with lymph node metastasis and it were in concordance withJamadar S *et al*[15]andYazdi*et al*[16] studies.

Histological grading has been used for many decades in an attempt to predict the biological behaviour of SCC in head and neck region. Broder[12] in 1920 initiated quantitative grading of carcinoma based on the differentiation of tumour cell. Later another histological grading system was introduced by Jacobsson[13] in 1973 which not only included morphological parameters but also included "mode," "stage of invasion," "vascular invasion" and "degree of lymphoplasmacytic infiltration" as additional criteria. His grading system has been modified by various authors like Fisher in 1975, Lund et al. in 1975, Willen et al. in 1975, Crissman et al. in 1980 and Anneroth et al. in 1987 as multifactorial grading systems.[8] Later Bryne et al[14]in 1989 further modified Anneroth grading system and presented a hypothesis suggesting that molecular and morphological characteristics at the invasive front area of various SCCs may reflect tumour prognosis better than other parts of the tumour. He proposed invasive tumour front (ITF) grading system better for predicting the prognosis for oral SCC.[7,8,11-14]

In order to further increase the accuracy of the grading system in predicting metastasis Depth Of Invasion was addedas an additional parameter in Bryne's grading system which showed most accuracy in comparison to any other grading system in predicting metastasis showing increase in predictive value from 58.3% to 64.1%.

Conclusion

In closing, our findings demonstrated that although the histopathological grading systems can be useful, reflecting on good and bad prognosis, no clear correlation between them was observed. Out of the four grading systems Bryne's grading system showed the most significant association with occurrence of metastasis. To strengthen the accuracy we added tumour depth of invasion as an additional parameter which showed excellent results enhancing the accuracy of Bryne's grading system in predicting metastasis.

Our study also demonstrates the importance of tumour depth of invasion as independent prognostic factor and its ability to strengthen grading system for prediction of metastasis in patients with Oral Squamous Cell Carcinoma.

References

1. Johnson NW, Jayasekara P, Amarasinghe AA. Squamous cell carcinoma and precursor lesions of the oral cavity: epidemiology and aetiology. Periodontol 2000. 2011;57(1):19-37.

2. Roh J, Muelleman T, Tawfik O, Thomas SM. Perineural growth in head and neck squamous cell carcinoma: A review.Oral Oncol. 2015;51(1):16-23.

3. Piffkò J et al. Prognostic value of histobiological factors (malignancy grading and AgNOR content) assessed at the invasive tumour front of oral squamous cell carcinomas. Br J Cancer. 1997;75(10):1543-6.

4. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck. 2005;27(12):1080-91.

5. Trehan SS, Patel K, Shukla HK, Tripathi U, Tadaiya M. The effect of depth of invasion and tumour size on risk of neck node metastasis in squamous cell carcinoma of oral cavity: retrospective analysis. Journal of Research in Medical and Dental Science. 2015;3(3):213-8.

6. Alkaisi A, Zaidan HA, Al Kabtan IA. The Predictive Value of Tumor Depth for Cervical Lymph Node Metastasis in Oral Squamous Cell Carcinoma; Prospective and Retrospective Study in Iraq. Journal of Cancer Science & Therapy. 2014;18:

7. Hosal AS, Unal OF, Ayhan A. Possible prognostic value of histopathologic parameters in patients with carcinoma ofthe oral tongue. Eur Arch Otorhinolaryngol1998;255:216–219.

8. Anneroth G, Batsakis J, Luna M. Review of the literature and a recommended system of malignancy grading in oral squamous cell carcinomas. Scand J Dent Res. 1987; 95(3):229–49.

9. Moore C et al. Thickness as Prognostic Aid in Upper Aerodigestive Tract Cancer.Arch Surg. 1986;121:1410-1414.

10. Woolgar J A. Histopathological prognosticators in oral and oropharyngeal squamouscell carcinoma. Oral Oncology. 2006;42: 229–239.

11. Wright JR Jr , Albert C. Broder's paradigm shifts Involving the prognostication and definition of cancer. Arch Pathol Lab Med. 2012;136(11):1437-46.

12. Broders AC. Squamous-cell epithelioma of the lip: a study of five hundred and thirty-seven cases. J Am Med Assoc. 1920;74(10):656-64.

13. Jakobsson PA, Eneroth CM, Killander D, Moberger G, Martensson B. Histologic classification and

grading of malignancy in carcinoma of the larynx. Acta RadiolTher Phys Biol. 1973; 12(1):1-8.

14. Bryne M et al. New malignancy grading is a better prognostic indicator than Broder's grading in oral squamous cell carcinomas. J Oral Pathol Med. 1989;18(8):432-7

15. Jamadar S et al. Comparative study of various grading systems in oral squamous cell carcinoma and their value in predicting lymph node metastasis. Indian Journal of Dental Research 2014;5(3):357-363.

16. Yazdi I, Khalili M. Grading of oral cancer: Comparison of different systems with respect to lymph node metastasis in tongue squamous cell carcinoma. Arch Iran Med. 1999;2:87-92.

Legend Tables

Table 1: Logistic regression analysis of grading systems

Variables in the Equation

		B	S.E.	Wald	df	P-value	OR	95.0% C. I. for OR	
								Lower	Upper
Step 1[a]	Anneroth_Total	.195	.602	.105	1	.746	1.215	.373	3.955
	Bryne_Total	.487	.222	4.795	1	.029	1.627	1.052	2.514
	Jackobson_Total	-.378	.449	.710	1	.399	.685	.284	1.651
	Constant	-.447	1.673	.071	1	.789	.640		
Step 2[a]	Bryne_Total	.501	.219	5.235	1	.022	1.650	1.074	2.535
	Jackobson_Total	-.244	.164	2.205	1	.138	.783	.568	1.081
	Constant	-.456	1.673	.074	1	.785	.634		
Step 3[a]	Bryne_Total	.250	.121	4.270	1	.039	1.284	1.013	1.627
	Constant	-2.344	1.154	4.122	1	.042	.096		

Table 2: Relationship of tumour depth with nodal metastasis, taking 7.1 mm as a cutoff

		Meta		
		PN+VE	PN-VE	Total
DOI_C	Positive (>7.1 mm)	23	9	32
	Negative (<7.1 mm)	7	21	28
Total		30	30	60

Graph 1: Stepwise multivariate logistic regression analysis for Depth of Invasion
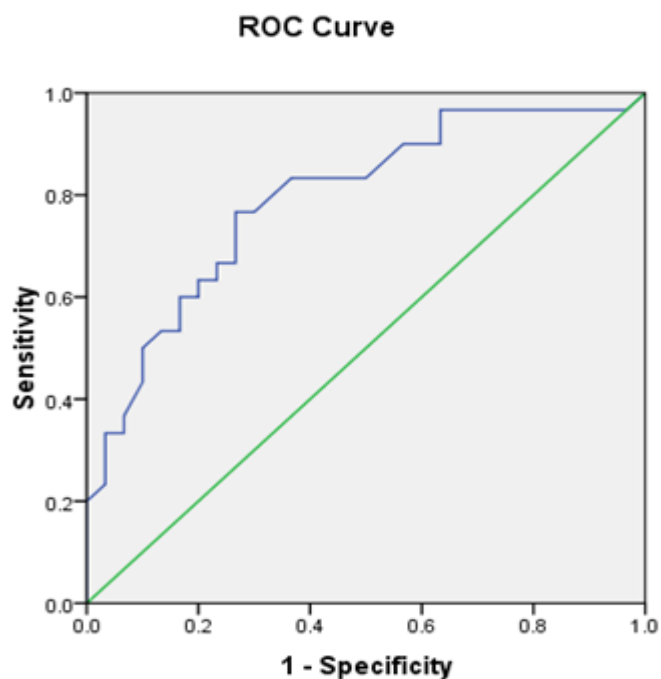

Figure 1: Methods of measuring tumor thickness: (A–D) tumor surface/base of the ulcer—deepest point of invasion (B–E) adjacent intact mucosa—deepest point of invasion (C–F) basal membrane—deepest point of invasion.
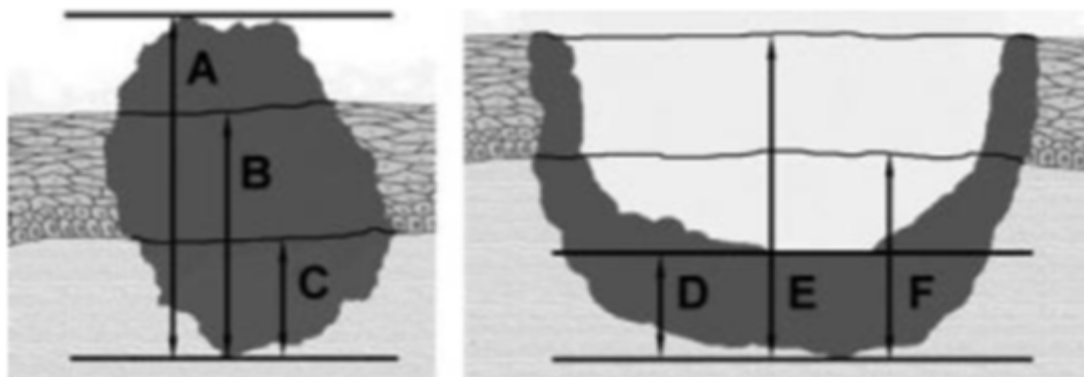
Figure 2: Measurement of depth of invasion: From the surface of epithelium up to the deepest point of invasion