STUDY ON HISTOLOGICAL GRADING OF ORAL SQUAMOUS CELL CARCINOMA AND ITS CO-RELATIONSHIP WITH REGIONAL LYMPH NODE METASTASIS

Pathology

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ABSTRACT

Introduction – Oral squamous cell carcinoma has a great predisposition to produce metastasis in lymph nodes. In clinical practice, the treatment plan and prognosis of oral squamous cell carcinoma is mainly based on the primary tumor, regional lymph node metastasis, and distant metastasis (TNM) staging system. However, this system does not provide any information on the biological characteristics and thus an aggressive clinical behavior of the tumor. There are many different grading system, out of which Broder's, Anneroth's & Bryne's systems were correlated with regional lymph node metastasis.

Aims & Objective – To study the grading of histological malignancy according to different grading classifications of biopsy specimens in relation to metastasis in the cervical lymph nodes.

Materials & methods – A retrospective study of 2 years with 48 cases of oral squamous cell carcinoma was taken. All cases were treated with wide excision of growth with radical neck dissection, registered between 2016 – 2018 in the Sunrise diagnostic lab, Gwalior were studied retrospectively.

Results – Surgical specimens of 21 metastasizing tumors were compared with 27 tumors which did not metastasize. Each case was graded according to: Broders' classification in the whole thickness of tumor, Anneroth's multifactorial grading system and Bryne's deep invasive cell grading system. Bryne's deep invasive cell score showed significant relation with lymph node metastasis. Other grading methods failed to show significant relation with metastasis. Bryne's deep invasive cell grading system in appropriate biopsy specimens would be of great value in predicting lymph node metastasis and treatment results of oral squamous cell carcinoma.

KEYWORDS

Bryne's, grading systems, metastasis, oral SCC

INTRODUCTION

Oral cancer represents the third most common form of malignancy in the developing countries, whilst in the developed countries it is the eighth most common form of cancer.[1] Oral squamous cell carcinoma (SCC) is the most frequent malignancy in the mouth, accounting to 95% of all oral malignant lesions. [2] The most affected sites are the tongue, inferior lips and floor of the mouth. The typical demographic profile of oral SCC is one of a man in the fifth to eighth decades of life, who is a tobacco chewer and/or a smoker. In India, where tobacco chewing is used with betel nuts and reverse smoking (placing the lit end in the mouth) is practiced, there is a striking incidence of oral cancer. [3] Less than 10% of cases arise in women.[4] Oral squamous cell carcinoma has a great predisposition to produce metastasis in lymph nodes. In clinical practice, the treatment plan and prognosis of oral squamous cell carcinoma is mainly based on the TNM (primary tumor, regional lymph node metastasis, and distant metastasis) staging system. The most recent staging system is the AJCC TNM staging system (2002)[5]. Staging is assessed by clinical methods with the aid of imaging techniques and Fine Needle Aspiration Cytology (FNAC). Staging aids in planning the course of management. However, TNM system does not provide any information on the biological characteristics and thus an aggressive clinical behavior of the tumor. There are many workers have devised histological grading systems to predict the biologic behavior of oral carcinoma like Broder's system (1927) [6], Jakobbson et al (1973) [7], Fisher (1975), Lund et al (1975), Willen et al (1975), Crissman et al (1980), Anneroth et al (1987) [6], Bryne's (1989, 1992) (ITF) Invasive Tumor Front Grading System Bryne M. (1998) [8]. Out of these different grading system, we have studied Broder's, Anneroth et al & Bryne's system of oral SCC and its co-relationship with regional lymph node metastasis.

MATERIALS AND METHODS

A retrospective study of 2 years with 48 cases of oral squamous cell carcinoma was taken. All cases were treated with wide excision of growth with radical neck dissection, registered between 2016 – 2018 in the Sunrise diagnostic lab, Gwalior, for whom adequate histologic material was available, were undertaken. The lesions that were primary tumor arising intra-orally, were included. The tumors that originated from the tongue, floor of the mouth, cheek, gingiva, palate, or retromolar trigone, were included. The tumors arising from the vermilion border of the lip, and the pharyngeal complex were excluded because these sites are not from the oral cavity proper. Tumors that involved the mandibular bone, overlying skin, resection specimens

following radiotherapy/chemotherapy, which reduce the bulk of tumor and obscure the cell morphology, and recurrent tumors; were all excluded from the study. General information including age, and sex were registered. The size of the primary tumor was noted and categorized into T1 to T3 (T4 tumors were excluded from the study), according to AJCC TNM stage for oral cavity and lip cancer. Number of involved nodes, and size of involved lymph nodes was noted, and categorized into NX to N3. [5] All the samples were fixed in 10% formalin, embedded in paraffin, and stained with Haemotoxylin and Eosin stain. The cases were reviewed and grouped into two categories based on lymph node metastasis into metastatic and non-metastatic. Cases in both the groups were graded according to the:

1. Broder's (1920) classification:

Accordingly, tumors were graded on the basis of degree of differentiation and keratinization of tumor cells into

Grade I: Well differentiated tumors – 75-100% of cells are differentiated

Grade II: Moderately differentiated tumors – 50- 75% of cells are differentiated

Grade III: Poorly differentiated tumors – 25-50% of cells are differentiated

Grade IV: Anaplastic tumor – 0-25% of cells are differentiated [6]

2. Anneroth's et al (1987) multifactorial grading system:

According to this system, three parameters reflecting tumor cell features including keratinization, nuclear pleomorphism, and mitoses were evaluated in the whole thickness of the tumor and each scored from 1-4 (Table 1). Pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration representing tumor-host relationship were graded in the most invasive margins and scored from 1-4. Then the sum of scores were grouped as follows: Grade I - 6-12, Grade II- 13-18, grade III- 19-24, and the results were compared in the metastasizing and non-metastasizing groups [6].

Table 1: Anneroth's et al (1987) multifactorial grading system for oral SCC's

Morphologic parameters	POINTS (SCORE)			
	1	2	3	4
Degree of keratinization	>50% cells keratinized	20-50% cells keratinized	5-20% cells keratinized	0-5% cells keratinized
Nuclear pleomorphism	Little	Moderately abundant	Abundant	Extreme

Number of mitosis/hpf	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well-delineated infiltrating borders	Infiltrating, solid cords,bands and/or strands	Small groups or cords of infiltrating cells	Marked and widespread cellular dissemination in small groups and/or in single cells
Stage of invasion	Carcinoma-in-situ and/or questionable invasion	Distinct invasion, but involving lamina propria only	Invasion below lamina propria, salivary gland tissues, and periosteum	Extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone
Lymphoplasmacytic infiltration	Marked	Moderate	Slight	None

3. Bryne's et al (1992) deep invasive cell grading system:

According to this system, number of mitosis and stage of invasion was omitted from the Anneroth's grading system, while the rest of the 4 parameters mentioned above were measured in the deepest invasive margins, and not in the whole thickness of the tumor, and graded similarly. The sum of scores were grouped as follows: Grade I- 4-8, grade II- 9-12, grade III- 13-16, and the results were compared in the metastasizing and non-metastasizing groups [8].

RESULTS

Reviewing a total of 48 cases of oral SCC reported during the study period between 2016 – 2018 treated with radical surgery and neck dissection remained for final analysis. Males were predominant comprised of 34 cases (70.8 %) with a male/female ratio of 2.4:1. 21 patients (43.7%) had lymph node metastasis and 27 cases (56.3%) were free of metastasis. Males in the metastatic group comprised of 13 cases with a male/female ratio of 1.6:1, while males in the non-metastatic group comprised of 22 cases with a male/female ratio of 3.5:1. Higher incidence of metastatic cancer in females is due to presentation with late nodal stage.

The mean age distribution was 53.2 with a range of 28 to 72 years. The mean age in males was 51.6 compared with 47.7 years in females. The mean age in males with metastasis was 49.5 compared with 51.4 years in females. The mean age in males with absence of metastasis was 50.2 compared with 46.3 years in females. There was no significant relation of age with lymph node metastasis.

The greatest diameters of tumors ranged from 1 to 5.1 cm with an average of 2.5 cm. With regard to primary tumor size, of the 21 cases analyzed in the metastatic group, 07 were T1 tumors, 12 were T2, and 02 were T3; while of the 27 cases analyzed in non-metastatic group, 18 were T1, 08 were T2, and 01 were T3. There was no significant relation of tumor size with lymph node metastasis.

The relation between Broders' classification and lymph node metastasis is shown in Table 2.

With regard to Broders' classification, of the 21 cases analyzed in the metastatic group, 08 were well-differentiated (Grade I), 11 moderately differentiated (Grade II), 2 poorly differentiated (Grade III) and 0 anaplastic (Grade IV); while of the 27 cases analyzed in non-metastatic group, 18 were well-differentiated (Grade I), and 09 moderately differentiated (Grade II). Statistical analysis failed to detect any significant relationship between Broders' grades and lymph node metastasis.

Table 2: A summary table of data showing tumors in the study as graded by Broders' classification

Broders' classification	Metastatic group No. (%)	Non metastatic group No. (%)	Total No. (%)
Well differentiated	08 (38.1)	18 (66.7)	26 (54.2)
Moderately differentiated	11 (52.4)	09 (33.3)	20 (41.6)

Poorly differentiated	02 (09.5)	00 (00.0)	02 (04.2)
Anaplastic	00 (00.0)	00 (00.0)	00 (00.0)
Total	21 (100.0)	27 (100.0)	48 (100.0)

With regard to Anneroth multifactorial grading system, of the 21 cases analyzed in the metastatic group, 06 were Grade-I, 14 were Grade-II and 01 Grade-III; while of the 27 cases analyzed in non-metastatic group, 20 were Grade I, and 07 Grade II (Table 3).

Statistical analysis failed to relate this grading method with lymph node metastasis.

Table 3: A summary table of data showing tumors in the study as graded by Anneroth multifactorial grading system

Anneroth multifactorial grading system	Metastatic group No.(%)	Nonmetastatic group No. (%)	Total No. (%)
Grade-I	06 (28.5)	20 (74.1)	26 (54.2)
Grade-II	14 (66.7)	07 (25.9)	21 (43.7)
Grade-III	01 (4.8)	00 (00.0)	01 (02.1)
Total	21 (100)	27 (100.0)	48 (100)

With regard to Bryne's deep invasive cell grading, of the 21 cases in the metastasizing group, 07 cases were grouped in grade I, 10 in Grade II and 04 in Grade III; while of 27 cases in the non-metastasizing group, 22 were grade I tumors, and 05 were grade II (Table 4). Bryne's score was the only significant predictor of metastasis.

Table 4: A summary table of data showing tumors in the study as graded by Bryne's deep invasive cell grading system

Bryne's deep invasive Cell grading system	Metastatic group No. (%)	Nonmetastatic group No. (%)	Total No. (%)
Grade-I	07 (33.3)	22 (81.5)	29 (60.4)
Grade-II	10 (47.6)	05 (18.5)	15 (31.3)
Grade-III	04 (19.1)	00 (00.0)	04 (08.3)
Total	21 (100.0)	27 (100.0)	48 (100.0)

DISCUSSION

Oral cancer is the commonest cancer in India, accounting for 50-70% of total cancer mortality.[3]

In our study on 48 oral SCC's, males comprised of 70.8% of cases. S P Khandekar et al [3] in their study on 80 cases of oral cancer, showed a prevalence of cancer in 61.25% of males and I. Yazdi et al in their study on 48 cases of tongue SCC showed male prevalence of 60.4% [9]. High proportion of cases among males may be due to high prevalence of tobacco consumption habits in them, coupled with smoking whereas in our society females less commonly indulge in tobacco smoking.

The current TNM classification is the widely used system for predicting the clinical result of oral SCC. In our study, T1 tumors lacking metastasis, showed statistical significance. However, a significant percentage (29 %) of patients with early stages of SCC (T1-T2) had shown a poor prognosis despite the small size of the tumor. Bundgaard et al demonstrated that up to 25% of patients with T1 could show poor prognosis at follow-up [10]. Thus, the TNM system includes acceptable prognostic parameters but the biological properties of the tumor cannot be predicted.

In the past, several investigators conducted studies on oral SCC's, correlating histologic malignancy grading with different clinical parameters such as clinical staging, recurrence and prognosis.

AC Broders' in 1920 initiated a quantitative grading system for the cancer of the lip. Broders' suggested that the grading of the tumors should be according to the differentiation of tumor cells. This system had four grades, of which grade 1 and 2 were relatively differentiated tumors, and grades 3 and 4 were not very well differentiated tumors. Despite the widespread use of this system, or slight modifications of it, there has generally only been a limited relationship with the grading and the outcome of treatment and survival of the patient. The suggested reason for such a poor correlation with the grading and prognosis, is the relative heterogeneity of the cell population present in the tumors.

In our study, and Yazdi et al[9] study, failed to observe any relationship

between Broders' system of grading and lymph node metastasis. Due to poor relationship between Broders' grading and patient survival, need for new system of grading was felt. It was recognized by many authors including Jakobsson, Eneroth, Moberger etc., that observing a number of factors in the biopsy along with cellular differentiation might give a better prognostic indicator of oral SCC. They also recognized that not only tumor cells, but also the reaction of the host to the tumor, needs to be graded to give more prognostic information.

Jacobsson et al (1973) multifactorial grading system was based on structure, differentiation, nuclear pleomorphism, mitosis, mode of invasion, stage of invasion, vascular invasion, and lymphoplasmacytic infiltration. After Jacobsson, many other researchers modified or developed new system based on the Jacobssons' grading system. These include Fisher (1975), Lund (1975), Willen (1975), Anneroth and Hansen (1984), Crissman (1980 & 1984).

In a comprehensive review of the above mentioned grading systems used in oral SCC's, Anneroth et al (1987) modified the existing multifactorial grading systems in use and proposed a new grading system. Unlike the previous systems where a number of parameters overlapped each other, this system reduced the number of parameters to be studied to keratinization, nuclear pleomorphism, mitoses, pattern of invasion, stage of invasion, and lymphoplasmacytic infiltration.

Dilana Duarte Lima Dantas et al[2] in their study on 16 cases of squamous cell carcinoma of the tongue, and I. Yazdi et al[9] in their study found no correlation between the Anneroth's histological scores of malignancy and the prognosis. In our study also, we failed to observe any relationship between Anneroth's multifactorial grading system and lymph node metastasis.

Anneroth and other multifactorial grading systems used the entire tumor cell population in a biopsy, to obtain a final grading of the tumor[6].

Bryne et al (1989) recognized the fact that there are heterogeneous tumor cell populations in malignancies, and observed that the cells in the deep invasive margin tend to be less differentiated than the cells in the superficial part of the tumor. Bryne et al in 1992 modified the grading system used by Anneroth. In Bryne's system, only the cells at the deep invasive margin of the tumor were graded. They also omitted stage of invasion and mitotic count from Anneroth's grading system, since their omission increased the reproducibility of the grading system. Also the validity of the mitotic count as a marker of prognosis remains controversial due to tumor heterogeneity, interobserver disagreement, variations in the size of the high power field in different microscopes and a too low mitotic count in the deep invasive parts of the tumor as compared with more solid tumor areas of tumors[8,11,12,13].

In our study the statistical relationship between Bryne's deep invasive cell grading system with lymph node metastasis was significant. I. Yazdi et al[9] & Doshi et al[14] in their study showed significant statistical correlation between Bryne's grading system and lymph node metastasis.

CONCLUSION

A significant percentage of patients with early stages of SCC have a poor prognosis despite the small size of the tumor [12]. Hence TNM staging system used in clinical practice does not provide information on the biological characteristic and aggressive clinical behavior of oral SCC. The first and most widely practiced grading system for oral SCC was developed by AC Broder.

Since then a multitude of multifactorial grading systems have developed. Jacobsson and Anneroth grading system, are still sometimes used and studied [1,6,7,12,13]. However, the most recent of these multifactorial grading systems developed by Bryne et al (1992) [8], which analyses four factors of the carcinoma in its invasive front is most reproducible but less popularly used. We found a significant positive trend between Bryne's deep invasive cell grading system with lymph node metastasis; while all the other grading systems, especially the most popularly used Broder's classification failed to show any statistical significance to lymph node metastasis.

In conclusion, we believe that Bryne's grading of the invasive parts of oral SCC could be taken as a valuable predictive factor in lymph node metastasis.

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