Grading of Oral Cancer: Comparison of Different Systems with Respect to Lymph Node Metastasis in Tongue SCC

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• Abstract

Background-Histologic grading has been used as a prognostic factor and for clinical behavior evaluation of oral squamous cell carcinoma (SCC) for the past several decades. At the same time, the prognostic value of different grading classifications remains controversial.

Methods-A retrospective study of 48 cases of tongue SCC was undertaken to compare different grading systems and their relation to lymph node metastasis. Surgical specimens of 22 non-metastasizing tumors were compared with 26 tumors which had metastasized. Each case was graded according to: Broders' classification in the whole thickness of tumor as well as deep invasive margins, multifactorial grading system (Anneroth et al. 1987), the Bryne et al. system (1989), and the new invasive margins grading method modified by Bryne et al. (1992).

Results-New malignancy grading based on the deep invasive margins showed significant relation with lymph node metastasis (p=0.03). Other grading methods failed to show any relation with metastasis.

Conclusion-Grading of the deep invasive margins in appropriate biopsy specimens would be of great value in predicting lymph node metastasis and treatment results of tongue SCC. Prospective studies with adequate follow ups are needed in order to obtain better evaluation of the role of this system in prognosis and survival.

• Keywords • Oral cancer • grading systems • metastasis • tongue SCC

Introduction

Intraoral SCC has a relatively unfavorable prognosis with a 35% to 50% of 5 year survival.1 Prognostic evaluation for OSCC is mainly based on clinical TNM classification, but this staging system is not sufficient for optimal prognostication and must be supplemented by other reliable methods.2,3 The histologic grading of tumors has been used for many decades in an attempt to predict the clinical behavior of SCC. The biological activity of oral SCC is evaluated and descriptively categorized as highly, moderately and poorly differentiated. This system was primarily developed by Broders. However, the classification of SCC, based on the differentiation or maturation of the tumor cell population alone, is of limited value as a basis for choice of treatment as well as for prediction of the outcome of the disease.2,3,4 Lack of correlation between Broders' grades and the prognosis of OSCC has been explained by the fact that SCC's usually exhibit a heterogenous cell population with probable differences in invasiveness and metastatic behavior.5 Since Broders' initial classification, multifactorial grading systems were introduced which were mainly based on different parameters of tumor cells as well as tumor-host relationship.3-6
Tongue SCC is the most common intraoral cancer in Iran. This study was undertaken to compare Broders' classification with three new methods of grading and their role in predicting lymph node metastasis in tongue SCC.

Materials and Methods

The archives of the Cancer Institute affiliated to Tehran University of Medical Sciences were used as the source of data collection. All cases of oral SCC's registered between 1981-1996 were studied retrospectively, and from a total of 875 oral SCCs, 375 cases of tongue tumor were selected. All pathologic and clinical records of the selected cases were reviewed and cases treated with hemiglossectomy with radical neck dissection were collected. Only patients for whom adequate histologic material was available or could be obtained were included in the study. To achieve a more homogenous sample material, some cases were excluded from the study. These comprised of tumors which had involved large parts of the floor of the mouth, the mandibular bone and adjacent structures, also cases in which base and surgical margins were not free of tumor. Finally, 48 cases of tongue SCC remained to be studied. General information including age, sex, past medical history, duration of disease, greatest tumor diameter and number and size of involved nodes were all registered.

Grading Systems:

For each case, the main slides containing the whole thickness of the tumor (including invasive margins) were used for histopathologic grading and each case was graded according to the following classifications:

1- Modified Broders' system (descriptive system); Accordingly, tumors were graded as well, moderately and poorly differentiated based on the degree of differentiation and keratinization of tumor cells.

2- For a multifactorial grading system, Anneroth et al.'s classification (1987), which was the last revision of the Jakobsson grading method (1973), was used. In this study, all parts of the tumors were apparently invasive and tumors with involvement of the bone and adjacent structures were excluded, so that the stage of invasion was omitted from the original grading system. According to this classification, three parameters reflecting tumor cell features including keratinization, polymorphism, and mitoses were evaluated in the whole thickness of the tumor and each scored from 1-4 (Table 1). Inflammatory infiltration and mode of invasion 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: 5-10 grade I, 11-15 grade II, 16-20 grade III and the results were compared in the metastasizing and non metastasizing groups.

3- An invasive margins grading system was performed as modified by Bryne et al. (1989) and the 5 parameters mentioned above were measured in the deepest invasive margins and graded similarly.

4- Based on the last modification of Bryne system in oral SCC's (1992) which has omitted mitoses from the grading methods, we excluded this parameter from the classification, so the sums of the scores were graded as 4-8 grade I, 9-12 grade II, 13-16 grade III. The results in the two studied groups were analyzed by SPSS package using Chi-square and T-student tests. When necessary, Mann-Whitney and Fisher Exact Test were used for statistical analyses using p<0.05 as a limit of significance.

Results

Reviewing a total of 357 cases of tongue SCC reported during the study period between 1981-1996 and excluding all unsuitable cases mentioned before, 48 cases of tongue SCC treated with radical surgery and neck dissection remained for final analysis. Males comprised 60.4% of cases with a male/female ratio of 1.5. The mean age distribution was 52.8 with a range of 18 to 75
years. The mean age in males was 52.3 compared with 53.8 years in females. Twenty-six patients (54.2%) had lymph node metastasis and 22 cases (45.8%) were free of metastasis. The male/female ratio in the former group was 1.2 compared with 2.2 in the later. This difference was not statistically significant revealing no relationship between sex and lymph node metastasis. The duration of the disease was available in 42 patients ranging from 1 to 42 months, with an average of 8.3 months. The difference of mean disease duration between the two studied groups was not significant (8.6 in metastasizing tumors and 7.9 in non-metastasizing ones.) Then, there was no relation between disease duration and lymph node metastasis.

The greatest diameters of tumors were considered measurable in 35 cases, ranging from 0.5 to 5.5 cm with an average of 2.4 cm. The difference between the two groups with respect to this parameter was also insignificant. So, in this study any relation between lymph node metastasis and the greatest diameters of tumors was not observed. The relation between Broders' classification and lymph node metastasis is shown in Table 2. Statistical analysis failed to detect any relationship between Broders' grades and lymph node metastasis.

The multifactorial grading system (Anneroth et al.) is shown in Table 3. Statistical analysis failed to relate this grading method with lymph node metastasis. Invasive margins grading was performed for all 48 cases. In metastasizing SCC's, 7.7% of the lesions were of grade I, whereas in the non-metastasizing group this figure rose to 31.8%. In the former group, 34.6% of cases were grade III tumors, whereas in the latter group 13.6% of cases were grade III (Table 4). These differences were statistically significant (P=0.05).

By omitting the original parameter "mitoses" from this classification, the statistical significance remained constant and reached 0.03. The relation between this classification and lymph node metastasis is shown in Table 5.

Discussion

Many studies on SCC's, correlating histologic malignancy grading with different clinical parameters such as clinical staging, recurrence and prognosis have been published, and a close relationship between the degree of histologic differentiation and the incidence of lymph node metastasis has been reported by several investigators. Broders initiated the quantitative grading of cancer in 1920 and his classification system has been used for many years. A lack of correlation between Broders' grading system and prognosis has been mentioned. One of the main reasons is that, SCC's usually exhibit a heterogenous cell population with differences in the degree of differentiation. However, Odell and his co-workers, in a study of small lingual SCC's, found a relationship between local recurrence and metastasis with Broders' grades. In our study we failed to observe any relationship between Broders' system of grading and lymph node metastasis. In 1973, Jakobsson et al. developed a multifactorial malignancy grading system in order to obtain a more precise morphologic evaluation of the growth potential of SCC's in the head and neck region. This malignancy grading system has been used during the last few years in both its original form and modified versions, especially for a retrospective study of SCC's. This system not only included an analysis of the carcinoma cell population,(the morphologic parameters "structure", "tendency to keratinization", "nuclear aberrations" and "number of mitoses"), but also an evaluation of the tumor-host relationship (as estimated by the parameters.
"mode and stage of invasion", "vascular invasion" and "the degree of lymphoplasmocytic infiltration"). To make morphologic criteria more precise, Anneroth and Hansen modified the grading system developed by Jakobsson et al. for application to SCC's in the tongue and the floor of the mouth. One of the parameters, "vascular invasion" was omitted. The clinical validity of the modified version of the classification was tested in a comprehensive study of 89 patients with SCC of the floor of the mouth. A statistically significant correlation was found between the mean total malignancy scores and clinical staging, frequency of recurrences and death. In our study, we used the Anneroth et al. classification but failed again to show any relation between lymph node metastasis and this grading system.

Recently, Bryne et al. introduced a multifactorial malignancy grading of only the deep invasive margins of oral SCC (Invasive Cell Grading = ICG) which proved to be of high prognostic value. The system applied was a modification of Anneroth's method, by grading the most invasive parts of the biopsies. In our study, this system was correlated with lymph node metastasis and showed a significant relationship. In the last modification of Bryne et al. classification, the parameter of "number of mitoses" was excluded and the prognostic value of invasive cell grading with and without mitotic counting was compared. Interestingly, the prognostic value remained highly significant and the reproducibility was slightly improved when the mitotic count was excluded from ICG.

In the present study, too, by excluding "number of mitoses" from the latest classification, the relation between the histopathologic grades and lymph node metastasis remained constant.

The validity of the mitotic count as a marker of prognosis remains controversial due to tumor heterogeneity, inter-observer disagreement, variations in the size of the high power field in different microscopes and also because the cell size is not taken into consideration. In addition, in grading of the invasive parts as in ICG, a too low mitotic count is recorded as compared with more solid tumor areas for tumors, with a high dissociation of cells. Recently, improved methods of estimating mitotic activity in solid tumors, such as in breast cancers have been published. The applicability of these methods to OSCC's remains to be studied.

Our study revealed the preference of ICG over Broders and multifactorial grading in the whole thickness of the tumor, with respect to the lymph node metastasis. This method is less time-consuming, as large parts of the tumors can be disregarded. A limitation of ICG is that biopsies are not necessarily representative of the whole tumor content, but since most oral SCC's are treated by irradiation, the biopsy is the only tissue sample available for evaluation. Despite some nonrepresentative biopsies, however, the prognostic value of ICG was shown to be highly significant in several studies. The clinical value of ICG will thus probably be further improved if larger pieces of biopsies are taken from the tumor. Generally, in the oral cavity, there are no contraindications for the removal of biopsies measuring 15×5×5 mm from representative areas. In most cases, this would be sufficient for ICG.

In conclusion, recent data indicate that cells at the invasive fronts in various human cancers reveal characteristics which correlate with tumor aggressiveness. Bryne et al. reported that the expression of a membrane-bound carbohydrate, blood group antigen H, is often lost in invasive tumor margins of OSCC's, and this is associated with poor prognosis. In addition, Kearsely et
al. found increased expression of proliferation-associated structures in the invading tumor margins of OSCC's. Similar observations have been made for H-ras and c-myc mRNAs. Such patterns have been described for other human cancers as well. In our study we observed less differentiated Broders' grades, decreased keratinization and an increased degree of polymorphism with marked tumor disassociation at the most invasive parts of tumors compared with more superficial parts.

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

References


