

RELATION OF HISTOPATHOLOGICAL PARAMETERS WITH UICC STAGING AND GRADING OF ORAL SQUAMOUS CELL CARCINOMAS

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SUMMARY

For finding more explanation about the behavior of oral squamous cell carcinomas (OSCC) many prognostic factors are being evaluated. Among these, tumor grade and stage are most widely accepted ones. Herein, in an attempt to find features correlated with tumor grade and stage, 16 histopathologic features, which may have prognostic significance, easily identifiable by light microscopy have been evaluated in a series of 36 cases.

The parameters we investigated in this study are: largest tumor dimension, depth of invasion, surface ulceration, degree of keratinization, nuclear pleomorphism, chromatin pattern, nucleolus prominence, mitotic and apoptotic indexes, growth of margin, necrosis, tumor vascularisation, peritumoral inflammation, desmoplasia, koilocytosis at the margin and tumor, pericapsular invasion in metastatic lymph nodes. These were scored and SPSS statistical program was performed for analysis of the relation of the above mentioned parameters with tumor grade and UICC stage. The statistical analysis showed strong correlation between UICC lymph node stage and pericapsular invasion ($p=0.0000$), also infiltrative growth pattern ($p=0.048$). Additionally, we obtained significant results in between some minor parameters. These findings suggest growth pattern at invasive margin should be described constantly for OSCC and a detailed search for metastatic foci at lymph nodes should be performed for cases with infiltrative growth pattern. Also perinodal invasion should not be neglected. As the series studied is small, other parameters needs further investigation.

Key words: Histopathologic parameters, oral squamous cell carcinomas.

ÖZET

Oral skuamöz hücreli karsinomaların (OSHK) davranışı ile ilgili daha çok bilgi edinmek amacıyla birçok prognostik faktör araştırılmıştır. Bunlardan tümör evre ve derecesi en fazla kabul görenlerdir. Burada, tümör evre ve derecesi ile ilgili, daha fazla prognostik bilgi sağlayabilecek, ışık mikroskobu ile kolayca tanımlanabilecek 16 histopatolojik özellik 36 olguda incelenmiştir.

İncelenen parametreler: En büyük tümör çapı, invazyon derinliği, yüzey ülserasyonu, keratinizasyon derecesi, nükleer pleomorfizm, kromatin paterni, nükleolus belirginliği, mitotik ve apoptotik indeksler, invazyon paterni, nekroz, vaskularizasyon, peritümöral inflamasyon, desmoplazi, tümörde ve çevrede koilositoz, perikapsüler invazyon ve metastatik lenf düğümleri. Parametreler skorlanıp SPSS istatistik programı ile tümör evre ve derecesi ile ilişkisi değerlendirildi. UICC lenf nodu evresi ile perinodal invazyon ($p=0.0000$) ve infiltratif büyüme paterni ($p=0.048$) ilişkili bulundu. Ayrıca minör parametreler arasında da anlamlı sonuçlar elde edildi. Bu bulgular invaziv kenardaki paternin OSHK'da daima tanımlanması gerektiğini ve bu patern infiltratif olduğunda da lenf düğümlerinde metastatik odağın ayrıntılı araştırılmasını vurgulamaktadır. Perinodal invazyonda önemle araştırılmalıdır. Çalışılan serinin küçük olması nedeniyle, diğer parametrelerin yorumlanması için daha geniş seriler gereklidir.

Anahtar sözcükler: Histopatolojik parametreler, oral skuamöz hücreli karsinoma

Prognostic factors are being searched for oral cavity squamous cell carcinomas (OSCC) like many other organ systems, in addition to

grading and staging which are known to have prognostic significance (1). Amongst these many histopathologic features have been

evaluated. And there is an ongoing search for finding parameters having prognostic value by sophisticated methods, like immunohistochemistry, molecular or cytogenetic studies (2). But still, most widely accepted method for routine diagnostic investigation is light microscopic examination by Hematoxylen and eosin (H&E). So, herein, in an attempt to find features correlated with tumor grade and stage (which have been accepted valuable for prognosis) for OSCC, we evaluated 16 features easily identifiable by light microscopy in a series of 36 cases.

MATERIALS and METHODS

36 patients with OSCC, who underwent radical surgery and neck dissection were studied retrospectively by means of examining the H&E stained slides from the archives of Dokuz Eylül University, School of Medicine, Department of Pathology. Site of origin were as follows: Tongue 18, buccal mucosa 8, gingiva 3, floor of the mouth 6, retromolar trigon 1.

Age, sex, UICC staging (3), grading (4) into well, moderate, poorly differentiated group depending upon degree of keratinization, pearl formation, presence of intercellular bridges formed by cancer cells, site of origin, the largest dimension of tumor (mm), depth of invasion using Breslow-type measurements excluding surface keratin layer (mm)(1), mode of invasion (infiltrative or expansive), tumor surface ulceration, lymphoplasmocytic infiltration and desmoplasia near tumor (scored 0 to 4 subjectively) were noted. Mitoses and apoptoses close to infiltrative margin were

counted in 1000 cells-HPF x400 (score 1= 0-10 mitoses, 2=11-20, 3= 21-30, 4=31-40, 5 =40 and more) as described previously (6). Degree of keratinization was scored as described by Bryne et al. as 0 for no keratinization, 1 for minimal keratinization (0-10 % of the cells), 2 for moderately keratinized (10-20 % of the cells), 3 for keratinized (20-50 % of the cells), 4 for highly keratinized (for >50% of the cells).

Nuclear pleomorphism was scored from 1 to 4 increasing with anaplasia. Chromatine pattern (coarse- fine), prominence of nucleolus (scored 1 when < 1/3 of nucleus, 2 when equal to 1/3 of nuclear diameter and 3 when > 1/3 of nucleus). Necrosis was scored as 0=no necrosis, 1=focal necrosis, 2=Necrosis larger than 1/2 HPF, 3=Necrosis larger than 1 HPF, 4=Extensive necrosis. Neovascularization in 10 HPF x400 (score 1= 0-2 microvessels, score 2=3-5 , score 3 =6-8, score 4=9-11, score 5 = >12 microvessels) was noted. Koilocytosis was also observed at the tumor and neighbouring mucosal epithelium.

Pericapsular lymph node invasion in metastatic lymph nodes was also determined.

Histologic grade, tumor stage and lymph node stage have been suggested to have prognostic significance (1). So, all the described parameters were analyzed in relation to grade and stage and between each other.

STATISTICAL ANALYSIS

The SPSS for windows statistical programme was used to analyze the results. The basic parameters (UICC tumor stage , node stage and histologic grade) were compared with other

possible parameters listed above. Also relation of all the parameters with each other were tested ($p < 0.05$).

RESULTS

The mean age of the patients was 55,33 (range,38 to 76). Twenty-four (66.66%) were males, 12 (33.33%) were females. Tumor stage was as follows: pT1= 11 cases (30.55%), pT2 =11 cases (30.55%), pT3 = 4 cases (11.11%), pT4 =10 cases (27.77%). Twelve patients were at the pN2, 5 cases pN1,19 cases pN0 (3). Tumor grade was as follows: Grade I, 21 cases (58.33%), Grade II, 7 cases (19.44%), Grade III 8, cases (22.22%). The mean tumor diameter was calculated as 29.30 mm (range, 5 to 70). The mean depth of tumor was 12.44 (range,2 to 40). Perinodal invasion was encountered in 12 patients (33.33%). Most of the tumors showed infiltrating margins (22 cases-61.11%). Surface ulceration was observed in 16 patients. Koilocytosis was found in only 4 cases (11.11%).

Statistical analysis revealed strong positive correlation between nodal stage and pericapsular invasion ($p=0.0000$) and weak with infiltrative growth pattern ($p=0,048$).

Among the other parameters, depth of invasion and apoptosis($p=0,014$) perinodal invasion and desmoplasia ($p=0,005$), nuclear pleomorphism and ulceration ($p=0,043$), degree of keratinization and inflammation (0,018) showed positive, growth of margin and koilocytosis ($p=0,018$) and chromatin pattern and prominency of nucleolus ($p=0,029$) showed negative correlation (Table I).

Table I: Statistical data of the parameters found to be correlated with each other analyzed by SPSS for windows statistical programme.

Histopathologic parameters	r	p
UICC lymph node stage- pericapsular inv.	,0000	,8659
UICC lymph node stage - growth of margin	,048	,3314
Depth of invasion- apoptosis	,014	,4056
Pericapsular invasion- desmoplasia	,005	,4616
Nuclear pleomorphism- ulceration	,043	,3393
Growth of margin- koilocytosis	,007	,4432
Degree of keratinization- inflammation	,018	,3924
Chromatin pattern- prominency of nucleolus	,029	,3636

DISCUSSION

Numerous studies of histopathologic features of tumor and patient response OSCC have shown variable prognostic significance (1,4). Broders et al (4) initiated the quantitative grading of tumors and applied those results to squamous carcinomas of the lip using parameters such as degree of keratinization, intercellular relationships, nuclear pleomorphism and number of mitoses. But later Bryne et al (6) found that invasive cell grading is a better independent prognostic parameter than conventional Broders' grading that is by grading only the deeper invasive margins of OSCC.

Jakobsson et al(7) recently proposed a scheme for laryngeal carcinomas including eight parameters; four reflecting tumor architecture (structure, differentiation, nuclear polymorphism and number of mitoses) and host response (mode of invasion, depth of invasion, vascular invasion and cell response). Jakobsson concluded that this scheme had greater

prognostic value than TNM staging. It is generally believed that mode of tumor invasion within the stroma and depth of tumor are the two important histopathological parameters (4,8,9). Crissman et al. (4) found when subjected to multivariate analysis, the pattern of invasion is a significant histologic feature that was more important than conventional tumor grade as a prognostic indicator. Consistent with this finding, the only parameter we could determine in this OSCC series about tumor morphology correlated to nodal stage is the invasion pattern. So when infiltrative pattern of growth is observed at the primary tumor, a detailed search for multiple metastases should be performed.

Klijanienko et al (2) studied in 114 consecutively recruited primary tumors (SCC) of head and neck prospectively. Tumor vascularization, differentiation and tumor emboli in the peripheral microvessel network were revealed as important histological parameters.

Guzman et al(10) revealed that capsule rupture and the number of metastatic lymph nodes were the only two parameters related to survival significantly. Adding the finding of the correlation between lymph node stage and perinodal invasion in this series, we can conclude that nodal staging of the TNM along with perinodal invasion determination are very important findings while, tumor stage is not a constant prognostic factor for OSCC.

Along with these features found prognostically significant in series concerning either oral or head and neck carcinomas, others not found important for patient survival have also been evaluated in this series including necrosis, ulceration, apoptosis, diameter of the nucleoli, nuclear chromasia, koilosis, desmoplasia, tumor diameter. Although significant results have been found between these minor parameters, none of these have been found to be correlated with UICC stage or grade. These can be evaluated in larger series correlated with prognosis, but from the results of these series, we only want to point out to the positive moderate correlation between perinodal invasion and tumor desmoplasia ($p=0.005$). As perinodal invasion is accepted as a poor prognostic factor, extensive desmoplasia may also be referred as an important feature about tumor morphology, related to prognosis.

We herein from a practical point of view, applied many possible histopathologic prognostic parameters easily identifiable by light microscopy to 36 OSCC and compared the results with UICC staging and histologic grading. Infiltrative growth pattern and perinodal invasion of tumor were significantly correlated with UICC lymph node staging. We strictly suggest description of the growth pattern for OSCC and detailed evaluation of lymph nodes for metastatic foci in cases with infiltrative growth pattern.

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