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THE PROGNOSTIC ROLE OF HISTOPATHOLOGICAL GRADE FACTOR IN PATIENTS WITH RESECTABLE ADVANCED ORAL SQUAMOUS CELL CARCINOMA

Abstract. Aim. To determine the prognostic significance of histopathological grade factor in patients with resectable advanced oral squamous cell carcinoma.

Object and methods. A retrospective analysis of the results of the treatment of 295 patients with resectable advanced oral squamous cell carcinoma was made. The analysis involved the patients who have undergone primary surgery with adjuvant radiotherapy or concomitant chemoradiation therapy.

Results. The multivariate analysis using Cox model revealed a significant impact (p=0.009) of high histopathological grade on overall survival, HR = 1.48 (95% CI 1.10 – 1.98); and the significant impact (p=0.003) of high tumor histopathological grade on disease-free survival, HR = 1.58 (95% CI 1.18 – 2.12). When comparing the curves of overall and disease-free survival, a statistically significant difference (p=0.001 and p<0.001, respectively, according to the logrank test) was found among the groups G1, G2, G3.

Conclusions. In our study, the high histopathological grade is an independent pathohistological factor of the poor prognosis in patients with resectable advanced oral squamous cell carcinoma. The overall and disease-free survival of patients in group G2 and group G3 was significantly lower compared to group G1. Further studies are needed to investigate the necessity for adjuvant CRT in patients with these pathological factors.

Keywords: oral squamous cell carcinoma, prognostic factor, pathohistological grade, overall survival, disease-free survival

Introduction: According to the National Cancer Registry of Ukraine, the incidence of oral cancer is 6.4 per 100,000 population. At the time of diagnosis in 2018, 50.7% of patients were detected in stages III-IV, while the mortality rate by the year was 41% [1]. Squamous cell carcinoma is the most common cancer and accounts for about 95% of all oral cavity malignancies. The development of oral squamous cell carcinoma (OSCC) is a multi-stage process modulated by genetic predisposition, tobacco and alcohol abuse, chronic inflammation and viral infections [2, 3]. Despite the significant improvement in the quality of life of OSCC patients, the overall 5-year survival rate has remained unchanged in recent decades [4].

In OSCC, there have been many efforts to identify factors that will allow staging in a way that accurately predicts prognosis [7].

The assessment of the pathohistological prognostic factors in patients with resectable advanced OSCC is quite important both in planning the adjuvant treatment strategy and in determining the prognosis of the disease [14]. A distinction is made between the pathohistological high-risk prognostic factors for relapse, such as positive resection margin, extranodal extension in the lymph nodes, and intermediate risk factors for relapse, such as pT3, pT4, lymphovascular invasion, perineural invasion, metastatic involvement of the cervical lymph nodes corresponding to pN2–3, metastatic lesions of the cervical lymph nodes of IV or V levels, and high histopathological grade [5,6].

The prognostic significance of such factors as the positive resection marging, extranodal extension is now recognized [5]. However, the final role of the histopathological grade factor remains unclear.

Aim of study: to determine the prognostic significance of histopathological grade factor in patients with resectable advanced OSCC.

Materials and Methods: We conducted a retrospective analysis of the results of the treatment of 295 patients with resectable advanced OSCC who were treated at the Head and Neck Oncology Department of the National Cancer Institute of Ukraine from 2008 to 2014. Oral cavity cancer subsites included: oral tongue cancer, lower alveolar ridge cancer, floor of mouth cancer, hard palate / upper alveolar ridge cancer, buccal cancer, retromolar trigonum cancer. The study included patients with resectable advanced OSCC who have undergone surgical treatment with adjuvant radiotherapy (RT) or concomitant chemoradiotherapy (CRT). The exclusion criteria for the study were immunotherapy, chemotherapy (CT) or RT, which were carried out before surgery; availability of distant metastasis; unresectable tumor; early stage disease (I-II stages) and tumor recurrence after prior treatment. The study protocol was approved by the Ethics Committee of the National Cancer Institute.

The disease staging was evaluated according to the International Union Against Cancer (UICC) 2002 tumor, node, metastasis (TNM) classification.

The study focused on such pathohistological factors as tumor histopathological grade, positive resection margin, extracapsular extension, multiple lymph node involvement, perineural invasion, lymphovascular invasion, tumor thickness, overall survival (OS) and disease-free survival (DFS). of patients depending on the histopathological grade (Group 1: G1-low grade, Group 2: G2-intermediate grade, Group 3: G3-high grade).

The statistical analysis of the results of our study was carried out in MedCalc v. 18.11 (Med Calc Software Inc, Broekstraat, Belgium, 1993-2018). The analysis of patient survival was performed using the Kaplan–Meier estimator. The logrank test was used to compare the survival curves. The hazard ratio (HR) was calculated from 95% confidence interval (CI) for OS and DFS. To evaluate the impact of several risk factors on survival (calculation of adjusted HR), a Cox proportional hazards regression model was used.

The Stepwise selection was used to select the independent factors of the multivariate models. The critical value in the analysis is accepted $\alpha cr = 0.05$.

Results: The study is based on the results of the analysis of 295 patients' medical records with resectable advanced OSCC. The gender distribution of 295 patients was as follows: the number of men was 263 (89.2%), women – 32 (10.8%). The average age of the patients was (56.8±8.9) years.

According to the localization of the disease, the distribution of patients was as follows: floor of mouth cancer – 75 (25.4%), tongue cancer was diagnosed in 141 (47.8%) patients, buccal cancer – 38 (12.9%), lower alveolar ridge cancer – in 18 (6.1%), hard palate/upper alveolar ridge cancer – in 5 (1.7%), retromolar trigonum cancer – in 18 (6.1%) cases.

According to T criterion, the distribution was as follows: T2 was established in 21 (7.1%) patients, T3 – in 187 (63.4%), T4 – in 87 (29.5%) cases.

The distribution according to N criterion: N0 was established in 104 (35.3%) patients, N1 – in 91 (30.8%), N2 – in 98 (33.2%), N3 – in 2 (0.7%) cases.

Stage III was established in 146 (49.5%) patients, while stage IV was established in 149 (50.5%) cases.

All 295 patients have undergone surgical treatment that included primary tumor removal, neck dissection and plastic replacement of postoperative oral defect with local, regional or free flap, or maxillary prosthetic repair.

The primary tumor was removed with a margin of 10 mm from the visible borders of the tumor. Resection results: R0 resection was achieved in 274 (92.9%) cases.

Supraomohyoid neck dissection was performed in 99 (33.5%) patients, modified radical neck dissection in 179 (60.7%), radical neck dissection in 15 (5.1%), extended neck dissection in 2 (0.7%) cases. Bilateral neck dissection was performed when the primary tumor was spread beyond the midline of the oral cavity or in the presence of clinical signs of metastatic involvement of the contralateral lymph nodes. Unilateral neck dissection was performed in 109 (36.9%) patients, bilateral – in 189 (64.1%) patients.

The plastic replacement of postoperative oral defects was performed using local, regional and free flaps depending on the type of defect. The local flaps were used in 22 (7.5%) patients, regional flaps – in 206 (69.8%), free flaps – in 62 (21.0%) cases. In 5 (1.7%) patients after maxillectomy, the defect was eliminated using prosthetic care.

After receiving the results of the pathohistological examination of the postoperative material, the pathohistological high-risk factors were diagnosed in 105 (35.6%) patients. Accordingly, the positive resection margin was established in 21 (7.1%) patients, extracapsular extension – in 84 (28.5%) cases.

The pathohistological intermediate risk factors were diagnosed in 190 (64.4%) patients: multiple lymph node involvement – 98 (33.2%), perineural invasion – 150 (50.8%), lymphovascular invasion – 183 (62.0%) of patients. The tumor thickness of 6-10mm was established in 106 (35.9%), 11-20mm – in 133 (45.1%), whereas more than 20mm only in 56 (19.0%) patients. The histopathological grade of the G1 tumor was established in 75 (25.4%), 184 – in 62.4 (%), G3 – in 36 (12.2%) patients.

The adjuvant CRT was prescribed to 105 (35.6%) patients who had adverse high-risk prognostic factors. 238 (80.7%) patients received a cumulative dose of cisplatin ≥ 200 mg/m2, while 57 (19.3%) patients had a cumulative dose of cisplatin <200 mg/m2.

The adjuvant RT was carried out in 190 (64.4%) patients who had adverse prognostic intermediate risk factors.

The average dose of RT was 58 Gy (range: 46-60 Gy).

All 295 patients began adjuvant treatment within 4-6 weeks after surgery.

The dynamic follow-up after combination treatment was carried out at intervals of 3 months for the first 2 years, followed by 1 every 6 months.

The survival rates of patients with resectable advanced OSCC who underwent primary surgical treatment with adjuvant RT or CRT are as follows: three-year OS and DFS was (64.3±2.8) and (63.2±2.8)%, respectively; five-year overall and DFS was (55.1±2.9) and (57.1±2.9)%, respectively.

The analysis of the prognostic impact of the pathohistological factors on DFS of patients. To take into account the impact of all pathohistological risk factors of relapse, the Cox multivariate approach was used. The Stepwise selection (critical rejection threshold 0.2 and critical inclusion threshold 0.1) was used to identify significant features. There were revealed 4 significant signs, such as the positive resection margin, extracapsular extension, multiple lymph node involvement and high tumor histopathological grade. The results of the analysis of the prognostic impact of the pathohistological factors on DFS in a multivariate model are presented in **Table 1**.

Table 1.

The multivariate analysis of the impact of the pathohistological factors on DFS in patients with resectable advanced OSCC.

Prognostic factors	Coefficient, b±m	p-level	HR (95% CI)
Positive resection margin	1.35±0,26	<0.001	3.87 (2.29–6.56)
Extracapsular extension	0.89±0.20	<0.001	2.43 (1.65–3.58)
Multiple lymph node involvement	0.93±0.20	<0.001	2.53 (1.71–3.73)
High histopathological grade	0.46±0.15	0.003	1.58 (1.18–2.12)

Note: *Coefficients of multivariable Cox regression models (b) and standard error (± m) are presented.

When conducting multivariate analysis, the relationship of DFS with the cleanliness of the resection margins ($p<0.001$) was found. The positive resection margins cause the increased risk of relapse, HR = 3.87 (95% CI 2.29 – 6.56) with standardization according to other risk factors. There was also found the relationship of DFS with the extracapsular extension ($p<0.001$). With extracapsular extension, the risk of relapse increases, HR = 2.43 (95% CI 1.65 - 3.58). The risk of relapse increases ($p<0.001$) in case of multiple lymph node involvement, HR = 2.53 (95% CI 1.71 – 3.73) with standardization according to other risk factors. The risk of relapse also increases ($p=0.003$) in case of higher histopathological grade, HR = 1.58 (95% HR 1.18 – 2.12) for each gradation with standardization according to other risk factors. The prognostic significance of perineural invasion, lymphovascular invasion and tumor thickness has not been established.

The analysis of the prognostic impact of the pathohistological factors on OS of patients. To take into account the impact of all pathohistological risk factors, the Cox multivariate approach was used. The Stepwise selection (critical rejection threshold 0.2 and critical inclusion threshold 0.1) was used to identify significant features. There were revealed 4 significant signs, such as the positive resection margin, extracapsular extension, multiple lymph node involvement and high histopathological grade. The results of the analysis of the prognostic impact of the pathohistological factors on OS in a multivariate model are presented in **Table 2**.

Table 2.

The multivariate analysis of the influence of the pathohistological factors on OS in patients with resectable advanced OSCC.

Prognostic factors	Coefficient, b±m	p-level	HR (95% CI)
Positive resection margin	1.39±0.27	<0.001	4.00 (2.36–6.78)
Extracapsular extension	0.94±0.20	<0.001	2.57 (1.75–3.79)
Multiple lymph node involvement	0.88±0.20	<0.001	2.41 (1.63–3.55)
High histopathological grade	0.39±0.15	0.009	1.48 (1.10–1.98)

Note: *Coefficients of multivariable Cox regression models (b) and standard error (± m) are presented.

When conducting the multivariate analysis, the relationship of OS of patients with the cleanliness of the resection margins was established ($p<0.001$), while with positive resection margins contribute to increased risk, HR = 4.00 (95% CI 2.36 – 6.78) with standardization according to other risk factors. The OS of patients with extracapsular extension ($p<0.001$) is associated with an increased risk of extracapsular extension, HR = 2.57 (95% CI 1.75 – 3.79). Also, the risk increases ($p<0.001$) in case of multiple lymph node involvement, HR = 2.41 (95% CI 1.63 – 3.55) with standardization according to other risk factors. The increased tumor histopathological grade increases the risk ($p=0.009$), HR = 1.48 (95% CI 1.10 - 1.98) for each gradation with standardization according to other risk factors. The prognostic significance of perineural invasion, lymphovascular invasion and tumor thickness has not been established.

The 5-year OS and 5-year DFS of patients with resectable advanced OSCC of varying histopathological grade are listed in **Table 3**.

Table 3.

5-year OS and DFS of patients with resectable advanced OSCC of varying histopathological grade.

Histopathological grade	5-year OS	5-year DFS
G I	69.3±5.3 %	75.4±5.1 %
G II	52.2±3.7 %	54.0±3.7 %
G III	38.9±8.1 %	35.7±8.1 %

The curves of the OS and DFS of patients with resectable advanced OSCC of varying histopathological grade are presented in **Figure 1.2**.

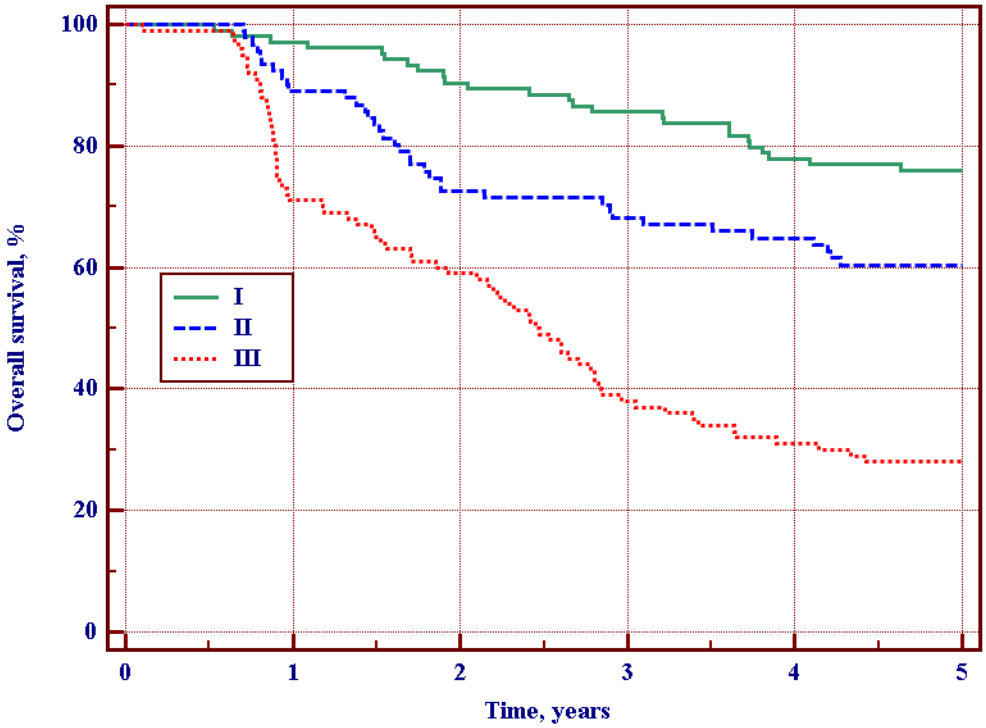

Figure 1.: The curves of the OS of patients with resectable advanced OSCC of varying histopathological grade
1 – G I: low grade
2 – G II: intermediate grade
3 – G III: high grade

When comparing the curves of the OS, a statistically significant difference (p=0.001 according to the logrank test) was found between the groups G1, G2, and G3. It was found that the increase in the histopathological grade is associated with a poor prognosis, so for the G2 group the relative risk index is HR = 1.89 (95% CI 1.29 – 2.76) compared to G1, for the G3 group – HR = 2,78 (95% CI 1.51 – 5.10) compared to G1.

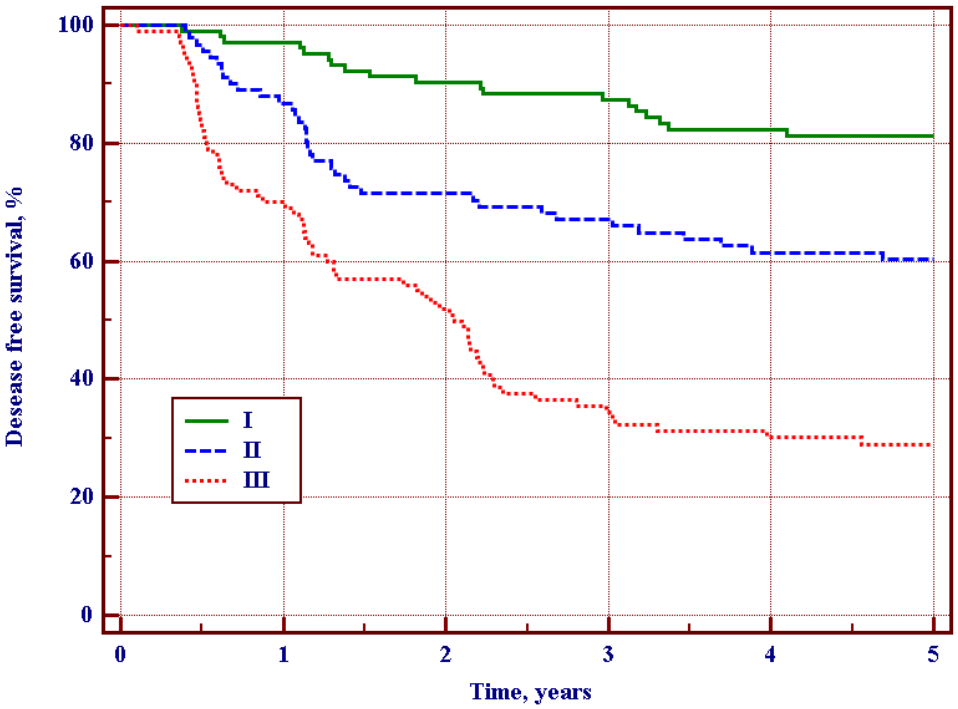

Figure 2.: The curves of the DFS of patients with resectable advanced OSCC of varying histopathological grade
1 – G I: low grade
2 – G II: intermediate grade
3 – G III: high grade

When comparing the DFS curves, a statistically significant difference ($p<0.001$ according to the logrank test) was found between the groups G1, G2, and G3. The increased histopathological grade increases the risk of relapse, so for the G2 group the relative risk index is HR = 2.36 (95% BI 1.52 – 3.35) compared to G1, for the G3 group – HR = 3.62 (95% BI 1.92 – 6.83) compared to G1.

Discussion: The assessment of the pathohistological prognostic factors in patients with resectable advanced OSCC is quite important both in planning adjuvant treatment strategies and in determining the disease prognosis.

If the independent prognostic significance of factors, such as the positive resection margin and extranodal extension, is considered recognized today, then the prognostic significance of the histopathological grade factor remains unknown.

The study of Y. Cheng and his co-authors, which included 8,986 patients, revealed that in the patients with all stages of OSCC who have undergone surgical treatment with adjuvant RT the histopathological grade was an independent prognostic factor, as well as a positive resection margin, extracapsular extension and advanced stage of the disease. The researchers also point out that the histopathological grade should be considered as significant in addition to the American Joint Committee on Cancer (AJCC) staging system when making clinical decisions [8].

In some literary sources, the histopathological grade has not been included in the assesment process at all, as it has not historically been identified as the prognostic factor [10].

In contrast, several studies have instead demonstrated that histopathological grade was an important prognostic factor, as was tumor size, extracapsular extension or the positive resection margin [6, 7]. Thus, the scientist Brandwein-Gensler M. and others suggest in their work that the recommendation for adjuvant RT should be based not only on traditional factors (positive margin, perineural invasion, bone invasion) but also on histologic risk assessment [6].

Also, researcher Brian Thomas notes that there is a strong association between histologic grade and survival in patients with stage I or II OSCC. [7].

Some studies focused on the histologic grade have found a correlation between the histopathological grade and survival. Their analysis reveals a statistically significant relationship between the histologic grading of the histopathological grade, tumor size, locoregional involvement, and survival rates [11].

Only a few studies have evaluated the pathohistological prognostic factors in patients with exclusively resectable OSCC of stages III-IV. The results of our study are most correlated with the results of researcher C. Liao and his co-authors, who proved that extracapsular extension, multiple lymph node involvement and high histopathlogical grade were independent prognostic factors in patients with resectable advanced OSCC. The researchers have not identified the effect of the positive resection margin on the survival rate of patients [12].

In the study by A. Noble and his co-authors, as well as in our work, the high histopatholohical grade significantly increased the risk of relapse in patients with resectable advanced OSCC [9]. The lymph node ratio, which in the above study also had a significant impacton relapse development, was not assessed in our study.

Our study revealed the same prognostic significance of the factor of high histopathological grade as the factors of the positive resection margin, extracapsular extension and multiple lymph node involvement. There was not found any prognostic significance of pathohistological factors, such as perineural invasion, lymphovascular invasion and tumor thickness.

Therefore, given the statistically significant negative impact of the high histopathological grade on the OS and DFS, we believe that further studies are needed to investigate the need for adjuvant CRT in patients with the specified pathologic factor.

Conclusions: In our study, the high histopathological grade is an independent pathohistological factor of the poor prognosis in patients with resectable advanced OSCC. The OS and DFS of patients of the G2 and G3 groups were probably lower compared to the G1 group. Further studies are needed to investigate the necessity for adjuvant CRT in patients with these histopathological factor.

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