

Tumor front grading in prediction of survival and lymph node metastases in patients with laryngeal carcinoma

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Abstract

Purpose: Despite innumerable both therapeutic and histopathologic studies that have been performed no morphologic markers are currently available in order to predict the outcome in patients with laryngeal cancer. According to the recent reports nowadays tumor front grading (TFG) is one of the most reliable methods of estimation of the progress of the changes in the peripheral part of tumor and it seems to be one of the techniques, which is able to assess the dynamics of the tumor growth quite precisely. In this study it was presented direct relation between morphological features of tumor front and survival.

Material and methods: The authors have analysed 120 cases of patients who were operated on the laryngeal squamous cell carcinoma in ENT Department Medical University of Łódź between 1995-2000. Features of the morphologic tumor front grading was performed on H&E-stained sections in the peripheral parts of a tumor. Dependence on tumor grade G, tumor size T, lymph node metastases and survival were analysed.

Results: Our study showed that feature such as TFG is very useful in prediction of survival in patients with laryngeal squamous cell carcinoma in comparison to the histological differentiation degree. The statistical analysis showed no significant correlation between TFG score and tumor size T, nodal status N and G feature.

Conclusions: The presented study emphasizes that TFG might influence decisions regarding therapeutic management and could eventually lead to more appropriate and individualized therapy. It is necessary to extend the traditional histopathological diagnosis by TFG, which assesses the dynamics of the malignant process and it seems to be a good prognostic

method in prediction of survival of patients with squamous cell carcinoma.

Key words: laryngeal carcinoma, tumor front grading, lymph node metastases, disease-free survival time, corrected actuarial survival.

Introduction

The cure rates of squamous cell carcinoma of the larynx have scarcely improved over past few decades. Despite innumerable both therapeutic and histopathologic studies that have been performed no morphologic markers are currently available in order to predict the outcome in patients with laryngeal cancer. The essential meaning of the estimation of the advance of the cancerous process and the choice of appropriate surgical treatment and prediction of survival and recurrences has been performed due to the histopathological examination [1-8]. This prognosis method considers only histological differentiation degree G and cancerous advance established on the basis of TNM classification. Traditional Broder's grading system, recently the most widely used method of staging disease, is not satisfactory in predicting survival and prognosis [1,3]. Scientists have been looking for a new diagnostic method, which could help to take a decision as to the basic and supplementary treatment, to predict metastases and survival, or the modification of already existing methods. According to the recent reports, nowadays tumor front grading (TFG) is one of the most reliable methods of estimation of the progress of the changes in the peripheral part of the tumor and it seems to be one of the techniques, which is able to assess the dynamics of the tumor growth quite precisely [4,8].

The purpose of this study was to analyse the tumor biologic factors in patients who were operated on the laryngeal squamous cell carcinoma and to determine the relationship between morphologic grading at the tumor front and the tumor grade

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Table 1. Features used for tumor front grading and numeric score

Features	Score points			
	1	2	3	4
Cytoplasmic differentiation	high (>50% keratinized)	moderate (20-50% keratinized)	poor (5-20% keratinized)	none (<5% keratinized)
Nuclear differentiation (polymorphism)	high (>75% mature cells)	moderate (50-75% mature cells)	poor (25-50% mature cells)	none (<25% mature cells)
Number of mitoses	single (0-1)	moderate number (2-3)	large number (4-5)	very numerous (>5)
Mode of invasion	well-defined bordeline	ords; less marked bordeline	groups of cells; no distinct bordeline	diffuse growth
Stage of invasion (depth)	possible invasion	microinvasion (few cords)	nodular into submucosa	invasion deeper than submucosa
Plasmalymphocytic invasion	marked (continuous rim)	moderate (many large patches)	slight (few small patches)	none

G estimated in the routine histology, tumor size T, lymph node N+ and N- and to the recurrence-free survival time and the corrected actuarial survival.

Material and methods

120 patients with histologically recognized squamous cell carcinoma were treated surgically from 1995 to 2000 in ENT Department Medical University of Łódź. The examination of these patients' specimens included routine histology and morphologic tumor front grading. Only the cases with follow-up at least 24 months were included.

In order to routine histology paraffin sections were stained with hematoxylin and eosin (H&E) and examined by the pathologist. Tumor were graded according to morphologic differentiation as grade G1 – well differentiated, grade G2 – moderately well differentiated, grade G3 – poorly differentiated and grade G4 – undifferentiated.

Morphologic tumor front grading was performed on H&E-stained sections in the peripheral parts of a tumor. We analysed the following features in the most invasive zones of the tumor: the cytoplasmic differentiation, the nuclear polymorphism, the number of mitoses per high power field, the mode of infiltration, the depth of invasion and the plasmalymphocytic infiltration of tumor front. These factors were assessed in at least five different regions of the peripheral part of the tumor (x400). Each factor was graded according to a scale ranging from 1 to 4. The total morphologic tumor front grading score was computed as the sum of the six parameters, with maximum score of 24 points. To compare the survival with the TFG total score the patients were divided into 4 groups: 6-9 points, 10-13 points, 14-17 points and 18-21 points of TFG (Tab. 1).

The statistical analysis was performed to determine whether the TFG score is correlated with survival. All statistical analyses were carried out with the aid of the χ^2 test, Spearman's test, Mann-Whitney's test or t-Student's test. The corrected survival curves were calculated according to the actuarial method of Kaplan and Meier. In all cases, only p values of less than 0.05 were taken to indicate statistical significance.

Results

Specimens taken from 120 patients with laryngeal carcinoma (104 men, 16 women, with an average age of 57.4 years and age range from 39 to 74 years) were examined. All patients underwent surgery – 75 (62.5%) patients out of 120 underwent selective neck dissection (SND), 35 (29.1%) radical neck dissection (RND), mainly ipsilateral, 5 (4.2%) contralateral SND and ipsilateral RND next and 5 (4.2%) ipsilateral RND following ipsilateral selective neck dissection.

The patients were classified according to the basis of TNM Classification of WHO (1990) International Classification of Diseases for Oncology. In this study 70 (58.4%) patients presented supraglottic and glottic tumors, 35 (29.1%) transalaryngeal tumors, 10 (8.3%) supraglottic tumors and 5 (4.2%) glottic and subglottic tumors, with stages from II to IV represented. In the examined group there were 10 (8.3%) patients with T2 tumor, 25 (20.8%) with T3 tumor and 85 (70.9%) with T4 one. In the case of 45 (37.5%) patients out of 120 subclinical cervical adenopathy was not detected through histological examination of the removed tissues, and the remaining 75 (62.5%) patients with lymph node metastases stadium N1 in 25 (20.8%), N2 in 50 (41.7%) patients was evaluated. There were no patients with N3 nodal status.

The invasive squamous cell carcinoma was confirmed histologically in all cases. In the examined group there were 20 (16.7%) patients with G1 carcinoma, 55 (45.8%) in G2 and 45 (37%) in G3 carcinoma. The undifferentiated carcinoma was not observed.

In the present study the analysis of tumor front grading revealed that the most numerous of tumors were carcinomas with the average TFG score (10-13 points) – 44.5%.

The actuarial corrected survival for the total group of patients was 35.4% after 5 years of follow-up. Analysis of the influence of the TFG score on the actuarial corrected survival revealed that the tumor front grading had a significant impact on the prognosis of survival (Fig. 1). Analysis of each feature used for morphologic grading revealed that depth and mode of invasion had significant influence on corrected survival. Histopathologically proven diffuse invasion of the thyroid cartilage

Figure 1. Actuarial corrected survival for total tumor front grading (TFG) score

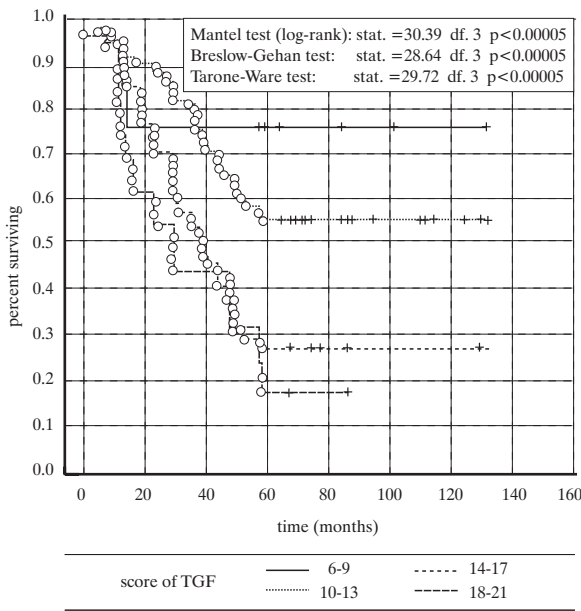


Figure 2. Actuarial corrected survival related to depth of invasion

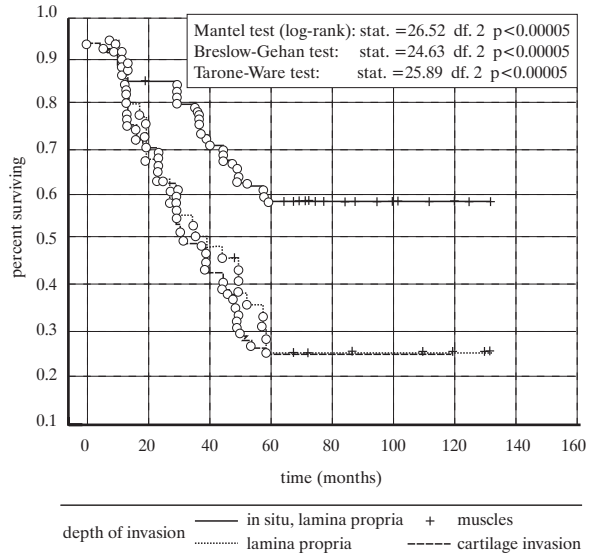


Figure 3. Actuarial corrected survival related to mode of invasion

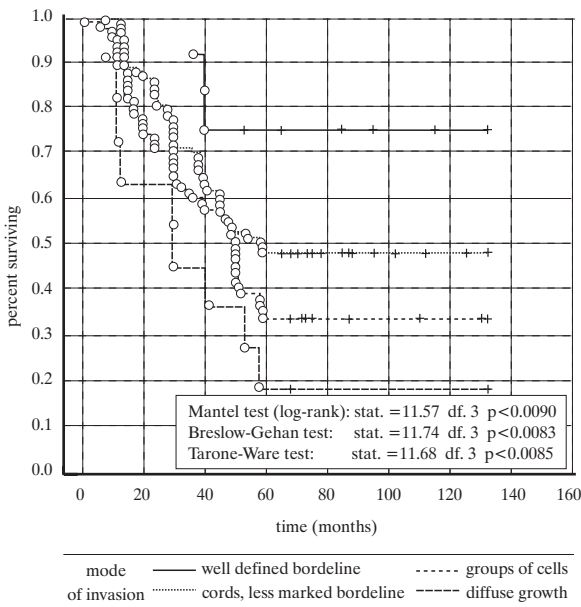
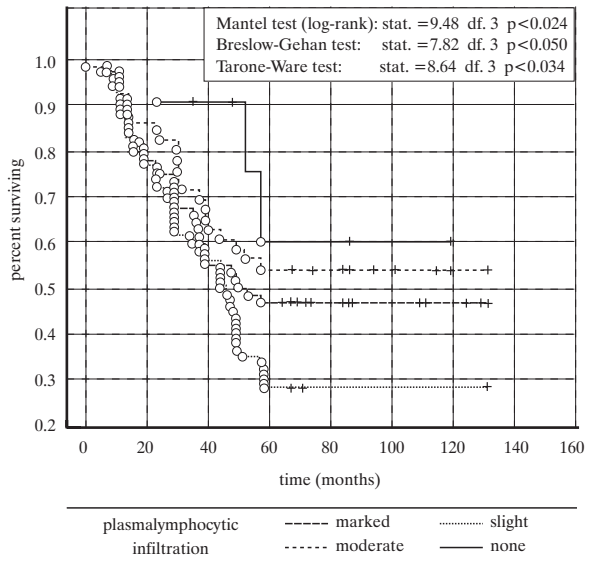


Figure 4. Actuarial corrected survival for plasmalymphocytic infiltration



resulted in a significant decrease in the corrected survival rate (Fig. 2, 3). The presence of plasmalymphocytic infiltration of the tumor space had a significant impact on the prognosis of survival as well (Fig. 4). Number of mitoses per high-power field did not demonstrate prognostic value on corrected survival (Fig. 5).

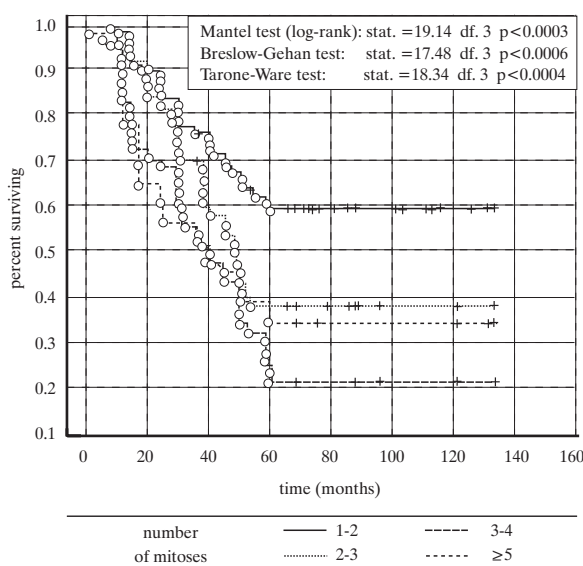
The patients were also divided into two groups. First of which was represented by patients with the recurrence-free survival time under 5 years – 90 (75%), and the second group with survival of 5 years and over 5 years – 30 (25%).

Our study showed that feature such as TFG is very useful in prediction of survival and recurrence in patients with laryngeal

squamous cell carcinoma in comparison to the histological differentiation degree. The mean number of points of TFG feature was 14.3 ± 3 (range 6 to 21). In 90 patients with survival under 5 years, TFG feature was meanly 12.1 ± 2.5 and in remaining ones with survival of 5 years and over 5 years TFG was 14.8 ± 3.2 . The difference between these both group was statistically significant ($p < 0.05$) (Tab. 2).

The statistical analysis showed no significant correlation between summary number of points for TFG and tumor size T and G feature. Only for G3 tumors TFG scores demonstrated higher values. The mean number of points of TFG for T4 was

Figure 5. Actuarial corrected survival for number of mitoses per high-power field



15.5±4.2, for T3 tumors was 14.4±3.1 and for T2 was 14.1±1.2, for G1 was 12.3±2.2, for G2 13.2±3.8 and for G3 tumors was 17.4±2.

No significant differences were found between TFG and neck lymph node status N. Mean number of points for group with subclinical cervical adenopathy (N+) and without lymph node metastases one (N-) was much the same and amounted for N+ 15.1±3.5 and for N- 14.8±4.

Discussion

From the factors relevant to prognosis of laryngeal carcinomas such as tumor site, tumor stage and nodal status, the last one is one of the most important traditional prognostic factors in laryngeal squamous cell carcinoma which influences the recurrence rate after the previous treatment [7-11]. However, on the basis of the several studies performed recently, biologic factors or host-related factors probably play the most important role in determining the eventual disease outcome [4-6,8,12].

Tumor front grading seems to be a good prognostic method of survival in patients with laryngeal carcinoma in comparison with traditional diagnostic methods [4,8]. Routinely used histologic differentiation degree has limited application because of only partly correlation with cancerous process [5]. In accordance with the results of TFG in squamous cell carcinoma of other sites such as oral cavity, tongue and breast the new malignancy grading system is used for both prediction recurrences and patient survival [2,13]. TFG is the technique, which assesses the dynamics of the tumor growth and provides multifactorial morphologic information about the carcinoma tissue. Cell differentiation, nuclear polymorphism, and number of mitoses are directly related to the biology of the tumor cells. Apart from elements of traditional histologic grading TFG also includes a type and depth of infiltration of the cancer, two elements,

Table 2. Dependence on G, T, N, disease-free survival time upon TFG

Feature	Number of cases (%)	TFG (+/- SD)
G1	20 (16.7)	12.3 (+/-2.2)
G2	55 (45.8)	13.2 (+/-3.8)
G3	45 (37.5)	17.4 (+/-2)
T2	10 (8.3)	14.1 (+/-1.2)
T3	25 (20.8)	14.4 (+/-3.1)
T4	95 (79.2)	15.5 (+/-4.2)
N+	25 (20.8)	15.1 (+/-3.5)
N-	50 (41.7)	14.8 (+/-4)
<5-years survival time	90 (75)	12.1 (+/-2.5)
≥5-years survival time	30 (25)	14.8 (+/-3.2)

which indicate the possibility of microfocal malignant invasion – the tumor aggressiveness. The lymphocytic infiltration might be related to the immunologic defense of the host.

Our results of the high correlation between TFG grading system and survival in patients with laryngeal cancer are in accordance with the other authors' results of tumor front grading in squamous cell carcinoma of other sites, including the oral cavity and tongue [2,4,8,13]. Therefore we suggest that prognosis should be determined by the biology of the cells at the most invasive zone of the tumor and it seems that histopathologic routine examinations should be extended by analysis of TFG as a supplement of traditional histologic estimation.

In histopathologic researches features as cell differentiation, nuclear polymorphism, number of mitoses, type and depth of infiltration appear as elements of many classifications and ranges of primary tumor [12-16]. Many authors have undertaken multifactorial morphologic valuation of the tumor in squamous cell carcinoma of other sites introduced similar conclusion [12-16]. Anneroth, Batsakis and Luna [14] separated the patients group with better prognosis using their own classification. Trial of prognosis in patients with laryngeal carcinoma undertake Jacobsson [12]. Author indicated total score in his classification is the prognostic factor and the most important features are nuclear polymorphism and mode of invasion. Zatterstrom [16] used Jacobson's scale has not proved relationship between histologic grading and clinical features. Crissman and Zarbo [15] proposed own modified morphologic scale and total score has the prognostic value. Other authors have not accepted Jacobson's and Crissman's classifications [13,17]. Lund [13,17] precisely defined every degree for histologic feature and proved that this scale correlated with survival and clinical disease course. Many researchers indicate the difference between central and periferal part of the tumor [4,8,15]. Welkoborsky [8] disclosed high correlation total score of tumor front grading with disease-free survival and local carcinoma recurrences. Similar conclusions introduced Gabriel [4] which estimated the necessity to add TFG to traditional histopatologic diagnosis.

The presented study emphasizes that TFG might influence decisions regarding therapeutic management and could eventually lead to more appropriate and individualized therapy. It is necessary to extend the traditional histopathological diagnosis

by TFG, which assesses the dynamics of the malignant process and it seems to be a good prognostic method in prediction of survival of patients with squamous cell carcinoma.

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