INVASIVE CELL GRADING – AN OVERVIEW*

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SUMMARY – Pathohistologic diagnosis plays a pivotal role in therapeutic modalities for cancer, and acts as a prognostic factor. The histologic grade is a numeric expression of tumor differentiation and is linked to patient outcome. Broders' scoring system is still widely used in scoring squamous cell carcinomas. New data suggest that in the most invasive parts of a malignant tumor, the morphology and biologic behavior differ from the central and superficial areas of the same tumor. A new invasive cell grading system has been proposed as a better prognostic factor in the multifactorial diagnostic and therapeutic approach to the patient with malignant tumor. Numerous studies performed to date have provided sufficient evidence to propose the invasive cell grading system to be introduced instead of the 'old' Broders' scoring system.

Key words: *Carcinoma – diagnosis; Carcinoma – pathology; Carcinoma – prognosis*

Introduction

Pathohistologic diagnosis is fundamental in the study of many diseases, tumors in particular. Therapeutic modalities for cancer can often rely upon diagnostic data provided by pathologists. Apart from the routine diagnostic procedure, histologic examination of the surgical specimen yields valuable data on the biologic behavior of the tumor.

On histopathologic assessment, many tumors are not graded or scored because sufficient information is associated with a specific diagnostic label. For example, cutaneous basal cell carcinomas are not graded because the diagnostic label and assessment of whether the lesion is excised are the only data required for the referring clinician to treat the patient.

In the majority of malignant tumors, the relation between the biologic behavior and the extent of differentiation is known for more than a century[1]. Subsequent observations on the characteristics of aggressive cancers had led to the 'histologic grade' concept, i.e. numeric expression of differentiation, which was linked to patient outcome. Broders' studies established a simple grading method for squamous cell carcinomas that is still widely used to the present[2-4]. By his grading method, tumors are assigned one of the four grades according to the percentage of tumor showing incomplete differentiation.

A grading or scoring system usually produces a single label that may be alphabetic or numeric. If the latter, it is important to recognize the attributes of the respective number. In most cases, the numeric label is an ordinal categorical label rather than a real number. This means that the label assigns the case to a particular group, and this group has a specific position in relation to other groups (e.g., grade 2 lies in-between grades 1 and 3). The majority of scoring systems combine several different features into a single score. In many cases, such summation reduces the amount of information valuable to the clinician receiving the report.

Many scoring and grading systems have been sufficiently well established and familiar to clinicians receiving histopathology reports, which they use extensively on making decisions on patient management. Several grading systems have been subsequently developed for tumors

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of various sites, just to mention some of the well established: Gleason score for prostatic carcinoma[5], Daumas-Duport grading for astrocytomas[6], International Federation of Gynecology and Obstetrics scoring method for endometrial cancer[7], Bloom and Richardson histologic grading of breast carcinoma[8], etc. In all their variations and modifications for specific site, the degree of differentiation is considered in relation to tumor biologic behavior.

It is a known fact that tumor morphology in the most invasive parts of a malignant tumor often is different from the central and superficial areas of the same tumor. At the invasive front, the tumor frequently shows a lower degree of differentiation and higher grade of cellular dissociation than the remaining areas of the tumor. This phenomenon is frequently observed in squamous cell carcinomas, malignant melanomas, and various adenocarcinomas (gastric, colorectal and prostatic).

The development of modern techniques in molecular pathology has confirmed that tumor cells at the invasive front of carcinomas differ substantially from the rest of tumor cells in a variety of human cancers[9,10]. Various molecular events of importance in tumor spread, such as the gain and loss of adhesion molecules, secretion of proteolytic enzymes, increased cell proliferation, and initiation of angiogenesis, occur at the tumor – host interface (invasive front).

Invasive Cell Grading

The features at the tumor – host interface have been summarized and simplified by Bryne *et al.*[11,12], proposing a new simple multifactorial malignancy grading system, i.e. *i*nvasive *c*ell *g*rading (ICG). Each of the morphological features: (a) degree of keratinization; (b) nuclear polymorphism; (c) number of mitoses *per* high-power field; (d) pattern of tumor invasion; and (e) lymphoplasmacytic infiltration, is given a score of 1 to 4 (score 4 being the worst feature). To increase the reproducibility of the scoring system in their subsequent modification, the counting of mitoses has been omitted[13].

Tumor cell characteristics are solely graded within the lowest differentiated parts of the most invasive 3-6 cell layers at the advancing front of the tumor. An average of 4 fields (magnification X100) are recorded as the score for each parameter. When the sum (total score) is achieved, the system recognizes three prognostic groups, i.e. good, moderate, and poor.

The grading is performed on routine H&E stained sections. No special stain is needed. The time needed for grading of one section is 1-3 minutes for a trained pathologist.

Discussion

In the last three decades, a number of studies have raised the question of the prognostic value of Broders' scoring system, as it takes into account the whole tumor area with no particular interest in the invasive front. It has resulted in the emergence of new scoring systems concentrating only on the tumor invasive front, scoring the features at the tumor – host interface[14-16].

The growing evidence that the invasive front grading system represents the prognosis better than Broders' system in head and neck tumors has been even more convincingly confirmed when combined with other methods. In oral squamous cell carcinoma, the argyrophilic nucleolar organizer regions-associated protein (AgNOR) content of invading tumor cells and the multiparametric histopathologic tumor front grade were found to be significantly and independently associated with tumor-related death, irrespective of the conventional Broders' grade and clinical stage of the tumors[17]. Strict correlation was found between the frequency and density of Ki67/p53 immunoreactivity according to ICG scores and poor patient prognosis[18]. Histologic characteristics of the deep invasive front have also proved to be a better indicator of prognosis than the T-category (size of tumor). The pattern of invasion and degree of keratinization were the strongest prognostic factors in multivariate analyses[19]. Broders' method of grading was compared with ICG grading system. Cox' multivariate survival analyses showed this new grading at the invasive sites to have a highly significant prognostic value, whereas Broders' grading had no prognostic value at all[14]. The usefulness of the deep invasive front grading system was also demonstrated for small lingual carcinoma[20].

The results of DNA analysis (2c deviation index, DNA malignancy grade) along with the morphologic tumor front grading and Ki67 score were closely related to prognosis ($p<0.01$). No correlation was found for Broders' grading or any other clinical parameter[21].

All these studies have shown that there are some more sensitive predictors of outcome in cancer patients (flow cytometry DNA analysis, use of molecular markers, immunohistochemistry, and other technologic procedures). However, compared with these methods, invasive front grading has established itself as an easily adopting, proven prognostic factor with practical advantages[22].

Clinicians and pathologists who prefer the 'simpler' Broders' system could argue that there is no point in producing more categories than there are treatment options available. But there is a more important counterpoint. If the response to treatment varies with a continuous feature such as differentiation, it is important to define as many grades of differentiation as possible in order to determine the precise relationship.

There must be a dialogue between the histopathologist and the clinician so that the role of the grade or score in patient management is understood and the clinician is aware of the degree of reproducibility of the system. The first duty of the pathologist is to extract as much information as possible from the surgical material and pass it on to the clinician.

The introduction and testing of such a new system is time-consuming but must be performed to ensure that histopathologists are transmitting real information in their reports, and not irrelevant 'noise', trying to help clinicians in making important therapeutic decisions.

The simple invasive cell grading has proved to be of high prognostic value and sufficient evidence exists to propose its introduction in clinical practice.

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Sažetak

STUPNJEVANJE INVAZIVNIH STANICA – PREGLED

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Patohistološka dijagnoza igra ključnu ulogu u terapijskom pristupu raku te djeluje i kao prognostički čimbenik. Histološki stupanj je brojčani izražaj diferencijacije tumora i vezan je uz prognozu tumorske bolesti u pojedinog bolesnika. Danas je u širokoj uporabi Brodersov sustav histološkog stupnjevanja u karcinomima pločastog epitela. Noviji podatci ukazuju na to da se morfologija i biološko ponašanje stanica u invazivnim dubokim dijelovima malignog tumora razlikuju od središnjih i površinskih dijelova istoga tumora. Novi sustav ICG (*invasive cell grading* – stupnjevanje invazivnih stanica) predložen je kao bolji prognostički čimbenik u složenom dijganostičkom i terapijskom pristupu bolesniku s malignim tumorom. Brojna su istraživanja potvrdila da se novi sustav ICG može s dovoljnom sigurnošću rabiti u patohistološkom stupnjevanju malignih tumora umjesto 'starog' Brodersovog načina.

Ključne riječi: *Karcinom – dijagnostika; Karcinom – patologija; Karcinom – prognoza*