A semi-quantitative World Health Organization grading scheme evaluating worst tumor differentiation predicts disease-free survival in oral squamous carcinoma patients☆

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ABSTRACT

We investigated World Health Organization (WHO) grading and pattern of invasion based histological schemes as independent predictors of disease-free survival, in oral squamous carcinoma patients. Tumor resection slides of eighty-seven oral squamous carcinoma patients [pTNM: I & II/III & IV-32/55] were evaluated. Besides examining various patterns of invasion, invasive front grade, *predominant* and *worst* (highest) WHO grade were recorded. For *worst* WHO grading, poor-undifferentiated component was estimated semi-quantitatively at advancing tumor edge (invasive growth front) in histology sections. Tumor recurrence was observed in 31 (35.6%) cases. The 2-year disease-free survival was 47% [Median: 656; follow-up: 14–1450] days. Using receiver operating characteristic curves, we defined poor-undifferentiated component exceeding 5% of tumor as the cutoff to assign an oral squamous carcinoma as grade-3, when following *worst* WHO grading. Kaplan-Meier curves for disease-free survival revealed prognostic association with nodal involvement, tumor size, *worst* WHO grading; most common pattern of invasion and invasive pattern grading score (sum of two most predominant patterns of invasion). In further multivariate analysis, tumor size (> 2.5 cm) and *worst* WHO grading (grade-3 tumors) independently predicted reduced disease-free survival [HR, 2.85; P = 0.028 and HR, 3.37; P = 0.031 respectively]. The inter-observer agreement was moderate for observers who semi-quantitatively estimated percentage of poor-undifferentiated morphology in oral squamous carcinomas. Our results support the value of semi-quantitative method to assign tumors as grade-3 with *worst* WHO grading for predicting reduced disease-free survival. Despite limitations, of the various histological tumor stratification schemes, WHO grading holds adjunctive value for its prognostic role, ease and universal familiarity.

1. Introduction

Oral squamous carcinomas (OSCC) management is guided predominantly by TNM staging [1-3]. With known limitations of pTNM staging [4], histological grading offers another window to decipher the biological behavior of OSCC [5].

For any OSCC exhibiting tumor heterogeneity, Royal College of Pathologists guidelines [5] accords core pathological status to the highest grade {worst differentiation at the invasive growth front [6]}, disregarding the value of the most prevalent grade (predominant differentiation in entire tumor). This is consequent to level B/C evidence on former's ability as a prognostic marker [5]. The conventionally followed WHO grading is based on the degree of tumor resembling native squamous epithelium [7]. However, instead of professing any value of this *predominant* tumor differentiation, WHO 'blue book' advocates recording the patterns of invasion (POI) at invasive growth front [7]. Thus, contradictory reports on value of WHO grading makes any oncologist wary of wading into this quagmire of uncertainty, during routine clinical practice.

On reviewing the literature, we observed that in most prior studies

grade-3 OSCC portends grave prognosis [8-12]. However, the majority of OSCC would be classified as either grade-1 or grade-2 tumors using predominant WHO grading [7]. It is also well known that even minor extent of poor-undifferentiated morphology at invasive growth front impacts prognosis adversely [6]. On joining the dots together, worst WHO grading performed at invasive growth front seemed to be of clinical relevance. Additionally, we hypothesized that a solution to this complex maze lay in estimating and defining the cutoff extent of poor-undifferentiated component in this region for classifying any OSCC as grade-3 tumor. Moreover, following this semi-quantitative methodology on resection specimen slides was expected to help improve inter-observer agreement and sampling related issues, known to occur in WHO scheme [13-14].

In the present scenario, newer histological schemes examining patterns of invasion like invasive front grading [15-16], histological risk assessment [9,17] and invasive pattern grading score [10] have been acknowledged to hold additional prognostic value.

The aim of the current study was to evaluate *predominant and worst* WHO grading and pattern of invasion based histological schemes, as independent predictors of disease-free survival (DFS) in an OSCC cohort.

2. Materials and methods

2.1. Patients selection

As per prevailing guidelines, Institution Ethics Committee approval was not required for this nonrandomized record based retrospective observational study. Between 2010 and 2014, eighty-seven (76 males and 11 females; Mean age: 47 ± 11 years) of the initially selected 100 consecutive cases of OSCC comprised the study cohort. Each of the OSCC case (gingivo-buccal-alveolus complex/tongue: 67/20) had undergone prior curative surgery and neck dissection. Microscopic tumor-factors were crosschecked. Only blocks & /or slides of tumor, which included invasive growth front were selected. Exclusion criteria included preoperative neoadjuvant chemo-radiotherapy, positive surgical margins or variant histology OSCC. As per TNM staging [18], there were 32 (36.8%) early stage (Stage I/Stage II: 10/22) and 55 (63.2%) advanced stage (Stage III/Stage IV: 16/39) cases. Regional node involvement (pN +), lymphovascular invasion, perineural invasion and extracapsular spread was observed in 43 (49.4%), 21 (24.1%), 39 (44.8%) and 14 (16.1%) cases respectively. The mean tumor size and depth was 30 (range: 5–80) mm and 10.7 (range: 1–24) mm respectively. Patients of the cohort were managed as per standard guidelines [1]. There was tumor recurrence in 31 (35.6%) cases and the mean follow up was 287 (range: 14–1450) days.

2.2. Histological evaluation (Fig. 1)

All the selected tumor sections were examined independently by two observers [Nikon microscopes, NiU]. The grading/tumor stratification schemes evaluated included: *predominant* and *worst* WHO grading, most common pattern of invasion (MC POI), worst pattern of invasion (WPOI), invasive pattern grading score (IPGS), histological risk assess-
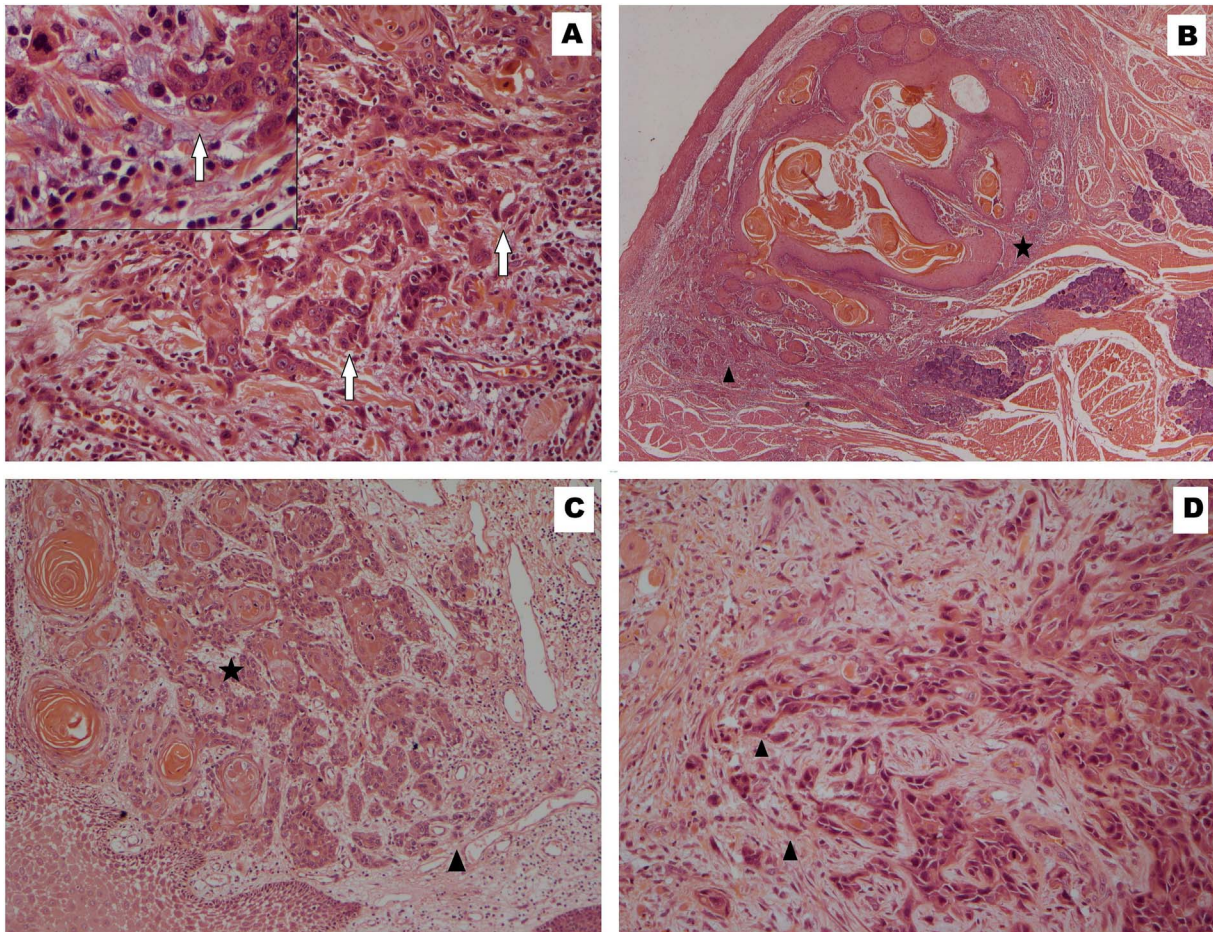

Fig. 1. Illustrative examples of methods followed for histological scoring in study cases. A [H & E, 200 × and 400 × (inset)], For *worst* WHO grading, poor-undifferentiated component (→) comprised 5% of tumor histology at invasive growth front (whole tumor not shown). Please note a mitotic figure (inset). B-C (H & E, 20 × & 100 ×), The most common (MC) pattern of invasion (POI)*, worst POI (WPOI▲) and invasive pattern grading scheme score (MC POI + second MC POI) score was: 1, 2, 1 + 2 and 2, 4, 2 + 3 respectively in two other carcinoma cases. D (H & E, 200 ×), WPOI▲ -4 had dissociated tumor groups of < 15 cells each.