Validation of the Risk Model: High-Risk Classification and Tumor Pattern of Invasion Predict Outcome for Patients with Low-Stage Oral Cavity Squamous Cell Carcinoma

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Abstract The Risk Model is a validated outcome predictor for patients with head and neck squamous cell carcinoma (Brandwein-Gensler et al. in *Am J Surg Pathol* 20:167–178, 2005; *Am J Surg Pathol* 34:676–688, 2010). This model may potentially shift treatment paradigms for patients with low-stage cancers, as current protocols dictate that they might receive only primary surgery. Here we test the hypothesis that the Risk Model has *added prognostic value* for low-stage

oral cavity squamous cell carcinoma (OCSCC) patients. 299 patients with Stage I/II OCSCC were characterized according to the Risk Model (Brandwein-Gensler et al. in *Am J Surg Pathol* 20:167–178, 2005; *Am J Surg Pathol* 34:676–688, 2010). Cumulative incidence and competing risk analysis were performed for locoregional recurrence (LRR) and disease-specific survival (DSS). Receiver operating characteristic analyses were performed for worst pattern of invasion (WPOI) and the risk categories. 292 patients were analyzed; 30 T1N0 patients (17 %) and 26 T2N0 patients (23 %) developed LRR. Disease-specific mortality occurred

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in 9 T1N0 patients (6 %) and 9 T2N0 patients (10 %). On multivariable analysis, the Risk Model was significantly predictive of LRR ($p = 0.0012$, HR 2.41, 95 % CI 1.42, 4.11) and DSS ($p = 0.0005$, HR 9.16, 95 % CI 2.65, 31.66) adjusted for potential confounders. WPOI alone was also significantly predictive for LRR adjusted for potential confounders with a cut-point of either WPOI-4 ($p = 0.0029$, HR 3.63, 95 % CI 1.56, 8.47) or WPOI-5 ($p = 0.0008$, HR 2.55, 95 % CI 1.48, 4.41) and for DSS (cut point WPOI-5, $p = 0.0001$, HR 6.34, 95 % CI 2.50, 16.09). Given a WPOI-5, the probability of developing locoregional recurrence is 42 %. Given a high-risk classification for a combination of features other than WPOI-5, the probability of developing locoregional recurrence is 32 %. The Risk Model is the first validated model that is significantly predictive for the important niche group of low-stage OCSCC patients.

Keywords Risk Model · Low-stage · Oral cavity · Pattern of invasion · Squamous cell carcinoma

Introduction

Patients with low-stage oral squamous cell carcinomas (OCSCC) are usually treated by surgery alone. Yet a certain percentage of these patients develop local recurrence and/or regional lymph node metastasis, and possibly disease-related mortality. There are few large studies of Stage I/II OCSCC that address this issue. Sessions reported disease-specific mortality rates of 25 and 37 % for Stage I and Stage II cancers, respectively [1]. Disease progression and disease-specific mortality rates of 12 and 3 %, respectively, were reported by Jerjes for Stage I/II patients [2]. Disease progression and overall mortality rates of 14.5 and 23.5 %, respectively, were reported by Huang for Stage I/II patients [3].

The Risk Model was originally proposed in 2005 [4] as an extension and modification of prior multivariable histological models [5–9] and was recently validated in a new patient cohort in 2010 [10]. The current study tests the hypothesis that the Risk Model has *added prognostic value* for low-stage OCSCC patients. These data can become the basis for predicting which low-stage patients are significantly at greater risk for locoregional recurrence. Thus low-stage high-risk patients, lacking the traditional indications

for adjuvant radiotherapy, may be offered the option of adjuvant radiotherapy based on this novel classification system.

Materials and Methods

With IRB approval, we identified 299 patients with Stage I/II primary OCSCC treated by *en-bloc* resection at University of Alabama at Birmingham (UAB), Tel-Aviv University (TAU), The Tom Baker Cancer Centre, University of Calgary (UC), Beth Israel Medical Center (BI), Montefiore Medical Center (MMC), University of Manitoba (UM), and New York University Langone Medical Center (NYU). The mechanism for identifying cases at each institution was identical. The pathologist from each center retrospectively reviewed reports on all consecutive head and neck resections, identified target index cases, and retrieved all pathology slides. For a number of sites (UAB, BI, NYU, and UM), it was feasible to continue prospectively identifying index cases. The cohort of 299 patients spanned over two decades (1989–2011) and included 95 patients with Stage I/II OCSCC who were previously reported in 2010 [10, 11] (MMC: $n = 44$, UM: $n = 24$, NYU: $n = 13$. TAU: $n = 14$), but herein have longer follow-up.

All hematoxylin and eosin stained pathology slides from the resection specimens were uniformly reviewed by MBG, blinded to outcome. All T1 carcinomas had been entirely submitted for histological evaluation. All T2 carcinomas were either entirely or nearly entirely sampled. Hematoxylin and eosin stained deeper levels were examined, when necessary, to resolve any issues. The following malignancies were excluded from study: SCC with depth of invasion under 1 mm, spindle cell variant of SCC, adenosquamous carcinoma, squamous carcinomas with prominent intraductal component, and patients who were seropositive for HIV. Verrucous carcinomas were not excluded, as they represent the prototypical “low-risk” SCC. There were only two verrucous carcinomas in this cohort.

All tumors were classified for perineural invasion (PNI), lymphocytic host response (LHR), and worst pattern of invasion (WPOI) according to previously published criteria, and then categorized according to risk level (Table 1) [10]. To avoid repetition, the details on how the these variables were assessed will be presented in the “Discussion”. Maximum depth of invasion was recorded on all carcinomas ≤ 1 cm. Resection margins were histologically assessed as follows: margins ≥ 5 mm from carcinoma were deemed negative; margins < 5 mm were deemed close and positive margins represented “tumor cut-through”.

Clinicopathologic and demographic information (medical center, age, gender, race, ethnicity, date of surgery, T stage, N stage, adjuvant therapy) were collected and coded

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Table 1 Face sheet for risk scoring

Variable	Definition	Point assignment
WPOI		
Type 1	Pushing border	0
Type 2	Finger-like growth	0
Type 3	Large separate islands, more than 15 cells per island	0
Type 4	Small tumor islands, 15 cells or fewer, per island	+1
Type 5	Tumor satellites, ≥ 1 mm from main tumor or next closest satellite	+3
LHR		
Type 1	Dense complete host response rimming tumor	0
Strong	Lymphoid nodules at advancing edge in each 4 $\times$ field	
Type 2	Intermediate host response	+1
Intermediate	Lymphoid nodules in some but not all 4 $\times$ fields	
Type 3	Little or no host response	+3
Weak	No lymphoid nodule	
PNI		
None	None	0
Small nerves	Tumor wrapping around nerves, <1 mm diameter	+1
Large nerves	Tumor wrapping around nerves, equal to or greater than 1 mm diameter (20 $\times$)	+3

A *lymphoid nodule* is defined as a dense collection of lymphocytes adjacent to carcinoma. Nodules are first identified at 4 $\times$, their density is then confirmed at 20 $\times$. The LHR should comprise at least 50 % of a 20 $\times$ field, immediately adjacent to carcinoma. Tonsillar tissue is excluded

WPOI-5: See “[Discussion](#)” for description. A simple method for microscopic measurement is overlaying pathology slides with millimeter rulers printed on acetate. (See http://www.vendian.org/mncharity/dir3/paper_rulers)

Add the total points from each variable for each case. If total point score = 0, then low-risk, if score = 1 or 2, then intermediate-risk, and if score = 3 or greater, then high-risk

WPOI worst pattern of invasion, **LHR** lymphocytic host response, **PNI** perineural invasion

in Microsoft Access databases. All surgeries were confirmed as being primary with curative intent. Adjuvant therapy consisted of radiotherapy; no systemic chemotherapy was administered in this low-stage cohort. Additionally, we collected information on alcohol and smoking on 191 and 217 patients, respectively. These data were categorized as (1) alcohol intake (yes/no), (2) ounces of alcohol per week, (3) smoking (yes/no), and (4) number of pack-years. The endpoints assessed were local recurrence and/or regional lymph node metastases (locoregional recurrence, or LRR), disease-specific survival (DSS) and overall survival (OS). LRR was measured from the initial surgery date

to the first pathologically documented LRR, versus last follow-up date with disease-free status. DSS was measured from the initial surgery date until disease-related death, versus last live follow-up date or death from causes other than index cancer. DSS was independently adjudicated in all seven medical centers by the physicians involved in the care of these patients. Patients with unknown cause of death were omitted from DSS analysis but included in OS analysis. Patients who were lost to follow-up were censored at the date last known to be alive. We do not expect the Risk Model to predict metachronous cancers; patients developing new primaries were censored at the date of diagnosis of a second tumor, and coded as disease-free with respect to the index tumor. The Microsoft Access databases were combined in Excel and deidentified for statistical analysis. Descriptive statistics was employed to summarize patient baseline characteristics, histological features and disease classification at diagnosis. Continuous data were summarized by using medians and ranges (min and max), categorical data by using frequency counts and percentages. The Chi square test was used for categorical variables, and the Wilcoxon rank sum test was used for continuous variables. Local recurrence and disease specific death are two time-to-event outcomes. The cumulative incidences curves were estimated in a competing risk framework [12]. For the analysis of local recurrence, we treated deaths from causes other than cancer as competing event; for the analysis of disease specific survival, we treated local recurrence and death from other causes as competing risk. The Gray test was used to assess the significance of differences in events across subgroups [12]. Both analyses were applied for the individual variables of WPOI, LHR, PNI, and the combined variables in the Risk Model. Other factors included medical center, gender, age ≥ 60 years, resection margin status, tumor stage, and treatment (surgery vs. surgery plus radiotherapy). All covariates adjusted for in the multivariable models were prespecified. Statistical analyses were carried out with SAS version 9.3 and the macro CumInc is used for estimation of the cumulative incidence function. Fine and Gray proportional-hazards model [13] for sub-distribution of a competing risk was used. The Receiver Operator Characteristics (ROC) analyses were performed for WPOI and the Risk categories, with respect to LRR and DSS. Alcohol and tobacco use was assessed for their influence on survival outcomes in a subset of data analysis. All reported *p* values are two sided, and statistical significance was claimed at ≤ 0.05 .

Results

The study group consisted of 299 patients with primary Stage I/II OCSCC; the clinicopathologic data regarding

Table 2 Characteristics of 299 patients with Stage I/II oral cavity squamous cell carcinoma

	Center							Total
	UAB	BI	TAU	UC	UM	NYU	MMC	
Number patients	69	52	44	27	35	23	49	299
Male (%)	62	54	55	59	54	39	65	56
Female (%)	38	46	45	41	46	61	35	44
Age range	29–87	29–89	34–89	28–90	36–84	33–94	41–95	28–95
Median age	60	64	64	64	65	60	64	63
Oral cavity								
T1 (%)	52	65	84	56	43	65	61	61
T2 (%)	48	35	16	44	57	35	39	39
Resection margin status								
≥ 5 mm (%)	48	67	71	81	43	39	59	59
< 5 mm (%)	46	13	23	15	54	48	31	33
Positive (%)	6	20	6	4	0	13	8	8
Unknown (%)	0	0	0	0	3	0	2	0
Treatment								
Surgery only (%)	90	73	59	74	74	35	71	72
Surgery + RT (%)	6	27	41	22	6	60	24	23
Unknown (%)	4	0	0	4	20	5	2	5

this cohort is summarized in Table 2. As can be expected in a multicenter study, there is heterogeneity in the methodology of margin assessment and the definitions of negative margins. This heterogeneity is reflected in the wide range for the rates of resection margin adequacy, defined here as ≥ 5 mm (39–81 %, median 59 %). The varying adjuvant radiotherapy rates also reflect different philosophies per institution (6–60 %, median 23 %). The frequency distributions for perineural invasion, pattern of invasion, lymphocytic response, and the risk categories, stratified for tumor stage are detailed in Table 3. The rate of high-risk tumors was significantly greater in T2 as compared to T1 tumors ($p = 0.042$), which was due to the significantly greater incidence of perineural invasion ($p = 0.0006$). Alcohol and smoking intake data was available on a subgroup of 191 and 217 patients, respectively. Smoking was common, the incidences varied from 30 % (Tel Aviv University) to 78 % (University of Alabama at Birmingham). Subgroup analysis of patients with available smoking and alcohol intake data, (191 and 217, respectively) demonstrated no association between smoking or alcohol use and either LRR or DSS.

Two hundred ninety-four patients were analyzed for outcome (average follow-up 31 months, Table 4). Thirty T1N0 patients (17 %) and 26 T2N0 patients (23 %) developed LRR (average 15 months). No patient developed distant metastasis as a first disease-progression event. Forty patients died; 18 patients (6 %) were independently adjudicated as having died of disease (average 14 months). DSS occurred in nine T1N0 patients (6 %) and nine T2N0

Table 3 Frequency distributions of risk variables per tumor stage

	Oral cavity		
	T1 (%)	T2 (%)	
Pattern of invasion			
Nonaggressive ^a	59 (32)	40 (34)	$p = 0.068$
WPOI4	101 (55)	52 (45)	
WPOI5	23 (13)	25 (21)	
Lymphocytic response			
Strong	41 (22)	23 (20)	$p = 0.240$
Intermediate	110 (60)	79 (67)	
Limited	32 (18)	15 (13)	
Perineural invasion			
None	153 (85)	78 (67)	$p = 0.0006$
Small nerves	29 (16)	37 (32)	
Large nerves	0 (0)	2 (2)	
Risk category			
Low	25 (14)	12 (10)	$p = 0.042$
Intermediate	102 (56)	56 (48)	
High	55 (30)	49 (42)	
Total	182	117	

^a Nonaggressive pattern of invasion encompasses WPOI1–3

patients (10 %) (average 14 months). All patients who died of disease had experienced prior LRR ($p < 0.0001$, Fig. 1). There was no significant association between LRR, DSS, and Stage. Twenty-two patients died of other causes.

Univariate analysis of LRR demonstrated that the following variables of interest were significantly associated

Table 4 Locoregional recurrence and disease-specific survival

Locoregional recurrence	Known outcome	Locoregional recurrence rate (%)	Median time-to event (months)
Stage I	177	17	11
Stage II	115	23	9
Disease-specific survival	Known outcome	Disease-specific mortality (%)	Median time-to event (months)
Stage I	161	5	13
Stage II	94	10	13

Fig. 1 Smoothed Hazard functions for survival outcomes: locoregional recurrence (blue line), disease specific death (red line), other deaths (green line). The figure demonstrates that in the first 20 months after treatment, the risks for both locoregional recurrence and disease specific death are highest. The risk of locoregional decreases steadily over time, while the risk of disease specific death decreases after a peak at 20 months. The hazard rate of death due to other causes continues to increase

with LRR: WPOI: $p = 0.0002$, LHR: $p = 0.0297$, and for the Risk Model which combined these variables: $p = 0.0012$. Analysis of DSS demonstrated that the levels of significance for the same variables were: WPOI: $p < 0.0001$, PNI: $p = 0.0301$, LHR: $p = 0.0269$, and the Risk Model: $p = 0.0001$ (Fig. 2). On multivariable analysis (Table 5) the Risk Model was significantly predictive of LRR (HR 2.41, 95 % CI 1.42, 4.11; $p = 0.0012$) and DSS (HR 9.16, 95 % CI 2.65, 31.66; $p = 0.0005$), when adjusted for medical center, gender, age ≥ 60 years, resection margin status, tumor stage, and treatment. WPOI as a single variable was also significantly predictive for LRR when adjusted for the same variables with a cut-point of either WPOI-4 (HR 3.63, 95 % CI 1.56, 8.47, $p = 0.0029$) or WPOI-5 (HR 2.55, 95 % CI 1.48, 4.41; $p = 0.0008$) and for DSS (cut point WPOI-5, HR 6.34, 95 % CI 2.50, 16.09, $p = 0.0001$). Table 6 demonstrates the sensitivities, specificities, negative predictive values (NPV) and positive predictive values (PPV) for WPOI and the Risk Model with respect to LRR and DSS.

Discussion

With the promise of prognostic molecular signatures still in its infancy, current treatment paradigms for patients with oral cavity squamous cell carcinoma (OCSCC) are based predominantly on tumor stage and patient performance status. Presently all OCSCC within each stage are treated identically, regardless of inherent differences in tumor biology. This is because histological variables such as tumor grade and degree of keratinization have not withstood statistical scrutiny as independent, validated prognosticators.

Tumor depth of invasion (DOI) has been studied extensively as a predictor of occult cervical metastases and disease-progression. Most studies support a cut-off value of 4–5 mm DOI; this value may be used as an indication for elective neck dissection [14–17]. Prior to the present study, there were no validated prognosticators for Stage I/II OCSCC beyond this 5 mm DOI cut-off. The Risk Model addresses this niche subgroup as a post-resection assessment that can be used to support the recommendation of adjuvant radiotherapy based on the weight of evidence. Multiparameter histological predictive models have been advocated in Europe since the 1970s and tumor pattern of invasion was a consistent component of these models [5–9, 18–22]. Other components have included lymphocytic host response, exophytic versus endophytic growth pattern, mitotic rate, degree of keratinization, and nuclear pleomorphism. Jakobsson's original model evaluated 8 variables in a 4- tiered scoring system. This cumbersome system was modified into a four-variable four-tiered system by Byrne [7–9]. Attempts at validating the Byrne model were not always successful. Problems included small sample size, heterogeneous tumor sites and primary treatment modalities, plus evaluation of different specimen types, as some studies evaluated only biopsies, others only resection specimens, and still others evaluated both biopsies and resection specimens. We published our novel Risk Model in 2005, which extended previous models and also contained some unique features [4]. The Risk Model classified patients into low-, intermediate-, and high-risk groups, and correlated significantly with locoregional

Fig. 2 Cumulative incidence curves for the endpoints of locoregional recurrence (*left*) and disease-specific survival (*right*) for the individual variables of worst pattern of invasion (WPOI), lymphocytic host response (LHR) and perineural invasion (PNI), and the Risk Model (Risk 1 = low-risk, Risk 2 = intermediate-risk, Risk 3 = high-risk), which represents the combination of these three variables. On univariate analyses, the greatest statistical significance is seen with WPOI, and with the Risk Model

recurrence ($p = 0.0004$) and overall survival ($p = 0.0001$). While the Bryne and Jacobsson models are linear, assigning equal weight to each variable, the Risk Model is non-linear, grouping together non-aggressive patterns of invasion, while assigning weighted point values for more aggressive features.

Here we demonstrate that the Risk Model is significantly predictive of LRR (HR 2.41, 95 % CI 1.42, 4.11; $p = 0.0012$) and DSS (HR 9.16, 95 % CI 2.65, 31.66, $p = 0.0050$) for patients with low-stage OCSCC. This makes a compelling argument for the value of our model. We believe that it is reasonable to offer low-stage high-risk patients the option of adjuvant radiotherapy based on the weight of evidence from this study. However, the present data could not demonstrate any outcome benefit for high-risk patients receiving adjuvant radiotherapy; this may be due to the small numbers of locoregional recurrences. Therefore, the logical next step would be a parallel Phase II

study comparing surgery versus surgery plus adjuvant radiotherapy for low-stage, high-risk patients, which would be designed to show promising clinical benefit.

From a practical viewpoint, Table 6 can be used as a “road map” with respect to predicting LRR. Given the presence of WPOI-5 in a Stage I/II OCSCC, the probability of developing LRR is almost 42 %. If a Stage I/II OCSCC is classified as high-risk based on a combination of features other than WPOI-5, for example PNI (score = +1), LHR-2 (score = +1), and WPOI-4 (score = +1), total Risk Score of +3, then the high-risk classification is still significantly predictive, but the probability of LRR drops to 32 %.

One study strength is that the cohort is large and geographically diverse. Another strength is the uniform application of the Risk Model, as all slides were reviewed by one of the investigators (MBG); substantial intrarater agreement ($\kappa = 0.77$, 95 % CI 0.61, 0.90) has been previously demonstrated [10]. Risk scoring is relatively simple as it is based on examining H & E stained slides from the adequately sampled tumor host interface. It needs to be reiterated that assessment of these histological features requires the study of resection specimens, not biopsies, as the advancing tumor edge is under-sampled in biopsies. Serial “bread-loafing” of the resection specimens is preferred, as it aids in the evaluation of WPOI (see below). T1 and small T2 OCSCC should be submitted entirely for

Table 5 Multivariable analyses for locoregional recurrence (LRR) and disease-specific survival (DSS) comparing patterns of invasion and the Risk Model

	Estimate	SE	<i>p</i> Value	Hazard ratio	95 % CI
LRR					
WPOI 5 versus others	0.937	0.279	0.0008	2.55	1.48, 4.41
WPOI 4–5 versus others	1.289	0.432	0.0029	3.63	1.56, 8.47
Risk categories	0.880	0.272	0.0012	2.41	1.42, 4.11
DSS					
WPOI 5 versus others	1.847	0.475	0.0001	6.34	2.50, 16.09
Risk categories	2.214	0.633	0.0005	9.15	2.65, 31.66

Results derived from a multivariable model which included medical center, age (>60), gender, resection margin status, T stage, and treatment (surgery vs. surgery and adjuvant radiotherapy)

Table 6 Receiver operator characteristics for LRR and DSS

	Locoregional recurrence				Disease specific survival			
	Sensitivity (%)	Specificity	NPV (%)	PPV (%)	Sensitivity (%)	Specificity	NPV (%)	PPV (%)
WPOI-3	100	0		18.7	100	0		6.0
WPOI-4	89.3	38.3 %	93.9	25.0	100	35.2 %	100	9.0
WPOI-5	35.7	88.5 %	85.7	41.7	55.6	86.5 %	96.8	20.8
Low-risk	100	0		18.7	100	0		6.0
Intermediate-risk	98.2	14.8 %	97.3	21.0	100	13.2 %	100	6.8
High-risk	58.9	70.8 %	88.2	31.7	83.3	68.3 %	98.5	14.4

histology. If a T2 OCSCC is close to 4 cm in size, then the advancing edge and resection margin planes should be submitted in entirety.

The goal of the initial publications [4, 10] was to describe the model and present the subsequent validation on a new cohort of patients, these publications were never intended to guide the practical application of the model. Presently, and prior to any clinical trial, there are surgeons at our institutions who believe that it is reasonable to offer low-stage high-risk patients the option of receiving adjuvant radiotherapy. Surgical pathologists at other institutions who would like to use the Risk Model should first seek out practical training sessions. Real-time multi-headed microscope training sessions improve the reproducibility between pathologists applying the Risk Model [10]. Below, we present some guidance regarding the application to the Risk Model, which is not intended to substitute for training sessions.

The Risk Model is based on the assessment of WPOI, LHR, and PNI; the definitions of these variables and scoring are summarized in Table 1. Figure 3 represents an algorithm for risk assessment. The point assignments are shown in yellow. As tumors with WPOI-1, WPOI-2, and WPOI-3 all receive the same score of 0, they are indicated in this figure as “Nonaggressive POI”. Nonaggressive tumors may have

either broad pushing fronts, or finger-like pushing fronts, or large (>15 cells) separated islands; the first two phenotypes are relatively rare compared to WPOI-3 tumors. Figure 4 illustrates phenotypes easily recognized as “Nonaggressive POI”. Tumors with nonaggressive POI can be considered *not to extend beyond their perimeter*. For example, tumors with interconnected “strand-like” islands (Fig. 5) or “finger-like” projections (Fig. 6) that are confined to a perimeter should be interpreted as “nonaggressive”.

WPOI-4 tumors are defined as having small tumor islands (≤ 15 cells per island) which are discontinuous, or *convincingly separated* from the main tumor mass; examples are illustrated in Figs. 7 and 8. WPOI-5 tumors are recognized by a dispersed, discontinuous growth pattern; the degree of tumor dispersion exceeds that seen for WPOI-4 tumors with a defined cut-off of 1 mm. The tumor dispersion distance may be measured between the main tumor and “the first wave” of dispersed satellites, or between subsequent, distal waves of satellites. A conservative approach should be adopted when assessing WPOI. When identifying putative WPOI-5 tumor satellites, it is preferable to examine the sections immediately adjacent to the area of interest, to exclude any connecting tumor projections. There are a number of possible histological phenotypes for WPOI-5 tumors; most commonly WPOI-5 tumors are dispersed

Fig. 3 Decision tree for evaluating WPOI, PNI, and LHR, and point assignment

Fig. 4 Low-power examples of some typical different phenotypes assigned as ‘Nonaggressive’ pattern of invasion (a–c). d Represents a medium power of the tumor in c. Some of these tumor islands may be detached, but they are large and confined within the tumor perimeter

Fig. 5 Medium-power view of an “interconnected strandy” tumor phenotype which remains confined to the perimeter and is therefore classified as nonaggressive POI. Contrast this phenotype with Fig. 8

throughout soft tissue either as tumor strands, small rounded tumor satellites, or large tumor satellites (Fig. 9). More rarely, tumors can be classified as WPOI-5 due to either dispersed perineural invasion (Fig. 10) or dispersed lymphovascular tumor emboli (Fig. 11). A simple method for microscopic measurement is overlaying the pathology slides

with millimeter rulers printed on acetate film (See http://www.vendian.org/mncharity/dir3/paper_rulers).

Perineural invasion is defined as carcinoma that specifically wraps around a nerve. Thus SCC adjacent to nerves, (or “bumping” against nerves) are excluded. Large nerves are defined as ≥ 1 mm in diameter.

Lymphocytic host response is assessed light microscopically at the advancing tumor edge, and is assessed cumulatively as the overall strongest response. LHR assessment presently does not require quantification of specific lymphocyte populations, however we have previously demonstrated that T cells are the predominant lymphocyte at the tumor advancing edge [23]. Figure 4a demonstrates a carcinoma with strong LHR throughout the advancing tumor interface. Here the LHR also extends into the carcinoma, but this is not requisite for LHR-1. The cut-point to separate LHR-1 and LHR-1 is that LHR-1 SCC has at least *one dense lymphoid nodule* per 4× field. A lymphoid nodule is defined as a dense collection of lymphocytes immediately adjacent to carcinoma which comprises at least 50 % of a 20× field, immediately adjacent to carcinoma (Fig. 12). A tumor with limited LHR has no identifiable lymphoid nodule (Fig. 13).

Fig. 6 Another example of nonaggressive POI. One may question if islands at the *arrowheads* can be considered as “convincingly separated”. A conservative interpretation is warranted in the context of this interconnected finger-like pattern. If no tumor islands/satellites are seen beyond the tumor perimeter, then it is classified as nonaggressive POI. If large islands (>15 cells) were seen beyond the perimeter, then it would still be classified as WPOI-3, or nonaggressive

In this study, we excluded small cancers with depth of invasion (DOI) under 1 mm. Twenty-six T1 OCSCC had DOI between 1 and 4 mm and none of these patients developed locoregional recurrence. However, limited depth of invasion is *not independent* of the Risk Model; all tumors with DOI of <4 mm were classified as either low-

Fig. 7 WPOI-4 tumor: The *top panel*, low-power, demonstrates convincingly separated tumor satellites beyond the tumor perimeter. The region in the rectangle is shown at higher power in the *bottom panel*, which demonstrates that some tumor satellites are <15 cells in size, warranting classification as WPOI-4

or intermediate-risk. Based on these data, we now conclude that it is reasonable to exclude invasive carcinomas with DOI of <4 mm from risk assessment.

Given the relative rarity of low-stage OCSCC, the only means of accruing a large cohort is to design a multicenter retrospective and prospective study. The pretreatment alcohol and cigarette intake data did vary in completeness; this might be considered relevant as some studies have demonstrated a dose-dependent relationship between pretreatment smoking and decreased OS [24]. However, for low-stage OCSCC, disease-specific mortality (DSM) is more relevant than OS and is very low in the present cohort. Subgroup analysis of patients with available smoking and alcohol intake data (73 and 64 %, respectively), demonstrated no association between smoking or alcohol use and either LRR or DSS. Therefore, it is highly unlikely that incompleteness of the smoking and alcohol data might have impacted our analysis. One study limitation is that data regarding intraoral subsite, and type of locoregional recurrence (local recurrence and/or regional lymph node metastases) were not uniformly collected from all seven centers. With respect to tumor subsite, previous unpublished analyses have demonstrated that the

Fig. 8 The *top panel*, low-power, demonstrates another example of a WPOI-4 tumor with a “strandy” pattern that clearly invades into the surrounding tissues without any perimeter or boundary. The *region in the rectangle* is shown at higher power in the *bottom panel*, which demonstrates that some tumor strands are <15 cells in size, warranting classification as WPOI-4

Fig. 9 WPOI-5: The *top panel*, low power, demonstrates an ulcerated T1 SCC with discontinuous dispersed islands. The *region in the rectangle* is shown at higher power in the *bottom panel* which demonstrates that the distance of the arrow is >1 mm, warranting classification as WPOI-5

distribution of risk categories varies with anatomic site, but the performance of the model is not affected. We recommend that follow-up studies address the above points.

A limitation of the current risk model is the fact that the definition of LHR is based on a specified size. Does the definition of a lymphoid nodule require adjustment for small T1 carcinomas? In the present study, 15 small T1

Fig. 10 The *green line* measures a distance >1 mm between the carcinoma and the next focus of dispersed PNI, warranting classification as WPOI-5

Fig. 11 The *top panel*, low power, demonstrates tumor dispersion through LVI. The *region in the rectangle* is shown at higher power in the *bottom panel*, which demonstrates that the green line measures a distance >1 mm between tumor emboli, warranting classification as WPOI-5

Fig. 12 *Top panel:* lymphoid nodules at the tumor interface. *The region in the rectangle is shown at higher power in the bottom panel, which demonstrates lymphocytes comprising >50 % of this $\times 20$ field immediately adjacent to carcinoma*

SCC were borderline LHR-2/LHR-3, these tumors were “upgraded” to LHR-2 (blinded to outcome) as they did not otherwise look like high-risk tumors. Figure 14 represents a schematic of these 15 LHR borderline patients. Based on these data, small T1 SCC ≥ 4 mm, with WPOI-3, no PNI, and borderline LHR-2/LHR-3, can be liberally upgraded to LHR-2. However, 2 of 7 patients with T1 SCC ≥ 4 mm, WPOI-4, no PNI, and borderline LHR-2/LHR-3 developed LRR. This highlights a potential problem area in the Risk Model, which requires further study.

Prior to the present collaboration, Vered et al. [11] published a cohort of 50 patients with oral SCC, all stages, evaluating the performance of the Risk Model. Multivariable analysis demonstrated that high-risk classification was significantly predictive of local recurrence when adjusted for confounders (age, margin status) ($p = 0.022$, HR 11.2, 95 % CI 1.4, 87.1). More recently, Rodrigues de Matos et al. [25] applied the risk model to 62 patients with tongue carcinoma, all stages; this study did not address the predictive performance of the model with respect to

Fig. 13 *This carcinoma is classified as limited LHR (LHR-3) as no lymphoid nodule is present at the advancing edge. The region in the rectangle is shown at higher power in the bottom panel which demonstrates limited lymphocytic infiltrate at $\times 20$*

outcome. They found that limited lymphocytic host response and perineural invasion correlated with positive cervical lymph nodes on presentation ($p = 0.034$, $p = 0.035$, respectively).

Conclusion

The Risk Model is the first validated model that is predictive for the important niche group of low-stage OCSCC patients. We report locoregional recurrence and disease-specific mortality rates of 20 and 7 %, respectively. The Risk Model was significantly predictive of LRR ($p = 0.0012$, HR 2.41, 95 % CI 1.42, 4.11) and DSS ($p = 0.0005$, HR 9.16, 95 % CI 2.65, 31.66) adjusted for potential confounding variables. Given a WPOI-5, the probability of developing locoregional recurrence is 42 %. Given a high-risk classification for a combination of features other than WPOI-5, the probability of developing

Fig. 14 Summary of 15 patients with borderline LHR 2/3

locoregional recurrence is 32 %. These data set the stage for the next logical step, which would involve a prospective, randomized Phase II trial to test the hypothesis that patients with low-stage high-risk cancers will benefit from receiving adjuvant radiotherapy. It is reasonable for surgeons to offer patients with low-stage high-risk SCC the option of adjuvant radiotherapy, based on the expectation that these patients are at greater risk for failing a primary surgical approach. However, we caution that surgical pathologists at other institutions who want to use the Risk Model should seek training sessions.

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