Histopathology

Histopathology 2016, **68**, 388–397. DOI: 10.1111/his.12754

Reproducibility and prognostic value of pattern of invasion scoring in low-stage oral squamous cell carcinoma

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Date of submission 3 March 2015
Accepted for publication 3 June 2015
Published online *Article Accepted* 8 June 2015

Heerema M G J, Melchers L J, Roodenburg J L N, Schuuring E, de Bock G H & van der Vegt B (2016) *Histopathology* **68**, 388–397. DOI: 10.1111/his.12754

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Aims: To evaluate and compare the prognostic value and reproducibility of different methods of pattern of invasion scoring in oral squamous cell carcinomas. The additional prognostic value to established histopathological prognostic factors was also analysed.

Methods and results: The study group was confined to 211 previously untreated patients who underwent surgery for low-stage oral squamous cell carcinoma between 1997 and 2008. Median follow-up was 64 months (range 0–193 months). Pattern of invasion was scored using five previously described methods, at random and independently, by two observers. Pattern of invasion scoring showed moderate interobserver reproducibility (Cohen's $\kappa = 0.52$–0.58). The predominant pattern of invasion and the summed predominant and worst pattern of invasion were independent prognosticators for locoregional recurrence-free survival (LRRFS) [hazard ratio (HR): 2.1, $P = 0.033$ and HR 2.2, $P = 0.024$, respectively] and disease-specific survival (DSS) (HR 2.3, $P = 0.032$ and HR 2.1, $P = 0.044$, respectively) in multivariate Cox regression analyses. The Harrell's C index for proven prognostic histopathological factors was 0.66 for LRRFS and 0.67 for DSS. This improved to 0.69 and 0.73 with the addition of pattern of invasion.

Conclusions: Pattern of invasion is an independent prognostic factor in low-stage oral squamous cell carcinoma. However, it has a moderate reproducibility, and the contributory value next to other prognostic histopathological factors is minimal.

Keywords: oral cancer, pattern of invasion, prognosis, reproducibility, squamous cell carcinoma

Introduction

Patients with low-stage oral squamous cell carcinoma (OSCC) are often treated with surgery alone. Neck treatment is offered to patients with clinical neck involvement only at the time of presentation, or to low-stage patients (stages I and II) who have a > 20% chance of having lymph node metastasis.[1–3] The presence of regional lymph node metastasis at presentation is the most significant adverse prognostic factor and a major determinant of poor survival.[4–7] However, up to 25% (stage I) and 37% (stage II) of patients with low-stage tumours who are treated with local surgery alone develop local recurrence and/or regional lymph node metastasis during follow-up, associated with disease-related mortality.[8–10] Therefore, more aggressive treatment protocols might be warranted in a subset of these low-stage patients.[10] According to current Dutch

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and international [British Association of Head and Neck Oncologists (BAHNO) and National Comprehensive Cancer Network (NCCN)] guidelines, positive resection margins, extracapsular lymph node extension and two or more tumour positive lymph nodes are major criteria for postoperative radiotherapy. Minor criteria are perineural growth, a marginal resection and a non-cohesive pattern of invasion (POI).[3]

Over the years many grading systems for the invasive tumour front have been developed, using histomorphological features such as degree of keratinization, nuclear pleomorphism, mitotic index, POI, stage of invasion and leucocyte infiltration.[4,9–17] The prognostic significance of invasive tumour front grading systems, and individual components of these systems, in squamous cell carcinomas of the oral cavity has been confirmed.[2,4,5,8,10,12–14,16–22] The most important factor in these grading systems is the POI at the invasive tumour front.[4,9,17] A major downside of these histopathological grading systems is that they suffer from significant inter- and intraobserver variability; previous studies have shown varying kappa values with regard to individual components of the invasive tumour front grading systems.[4,10,14] In this study we aimed to compare the interobserver reproducibility of the different scoring systems for POI. A second objective was to calculate the additional prognostic value of POI scoring to proven prognostic histopathological factors on locoregional recurrence-free survival (LRRFS) and disease-specific survival (DSS).

Materials and methods

PATIENTS AND MATERIALS

This study included a well-defined consecutive series of 211 patients with pT1–T2 tumours of primary oral location, as described previously by Melchers *et al.*[23] All patients had histologically proven squamous cell carcinomas, diagnosed between 1997 and 2008, and were treated in the University Medical Center Groningen by resection of the primary tumour without previous head–neck or systemic oncological treatment.[23] For all tumours, clinicopathological data regarding nodal status were available.

The previously published series consisted of 246 cases. For the current analysis, cases with synchronous multiple tumours ($n = 3$), irretrievable haematoxylin and eosin (H&E)-stained slides ($n = 13$) or unreliable assessment of infiltration depth, due to tangential sectioning ($n = 19$) were excluded. In June 2013, the follow-up of all cases was updated. The median follow-up was 64 months (range 0–193 months).

All H&E-stained slides were retrieved from the archives of our department. Some cases ($n = 33$) missed data regarding perineural growth and lymphovascular invasion. This was additionally evaluated.

All patient material was handled according to the 'Code of conduct for health research' of the Dutch Federation of Biomedical Scientific Societies.[24] Therefore, no additional permission from our Ethics Committee was needed.

NODAL STATUS, TREATMENT AND FOLLOW-UP

Preoperative clinical nodal status was assessed by palpation of the neck combined with imaging [computerized tomography (CT) and magnetic resonance imaging (MRI)] and, when indicated, positron emission tomography (PET) or ultrasound with aspiration cytology. Patients with a pathological T1, clinical N0 OSCC with low risk for nodal metastases did not receive surgical treatment of the lymph nodes. For these patients a watchful-waiting procedure (return visits every 6 weeks, with clinical assessment of the lymph nodes) was performed. Patients with pathological T1 tumours with clinically suspect or proven lymph node metastasis and all patients with T2 tumours received treatment of the neck, either with a sentinel lymph node biopsy or a supraomohyoidal lymph node dissection. For patients not receiving a neck dissection, at least 2 years of follow-up data were examined for the development of locoregional recurrence. Nodal metastases were initially diagnosed clinically (no routine imaging), and always confirmed using fine-needle aspiration cytology.

HISTOLOGICAL SCORING OF POI

The number of slides assessed for each case was variable and dependent upon the tumour size. In general tumours < 2 cm were totally embedded for microscopic evaluation. From tumours ≥ 2 cm stepwise cross-sections of the invasive tumour front were embedded. For each tumour all available slides with invasive carcinoma were scored regarding the growth pattern of the whole tumour in four categories; see Table 1A.[9] At the invasive tumour front, we scored the predominant pattern of invasion (PPOI), the second most predominant pattern of invasion (SPPOI) (cut-off $> 20\%$ of the invasive tumour front) and the worst pattern of invasion (WPOI). For the WPOI there was no minimal cut-off value; the presence of even one small tumour group

Table 1. Histological grading

(A) Histological grading of the whole tumour				
1	2	3	4	
Papillary and solid	Strands	Small cords and groups of cells	Marked cellular dissociation	
(B) Histological grading of the POI at the invasive tumour front				
1	2	3	4	5
Pushing, well-delineated infiltrating borders	Infiltrating, solid cords, bands and/or strands	Small groups or cords of infiltrating cells ($n > 15$)	Marked and widespread cellular dissociation in small groups of cells ($n < 15$) and/or in single cells	Tumour satellites of any size ≥ 1 mm away from main tumour or next closest satellite with intervening normal tissue[a]

POI, pattern of invasion.
[a]This fifth category was added by Brandwein-Gensler *et al.*[8,10,13]

($n < 15$ cells) or individual infiltrating tumour cell was considered positive, as described previously by Brandwein-Gensler *et al.*[8,10,13] If the SPPOI was < 20% of the invasive tumour front the score of the PPOI was used twice, as described by Chang *et al.*[14] The POI was scored in four and in five categories;

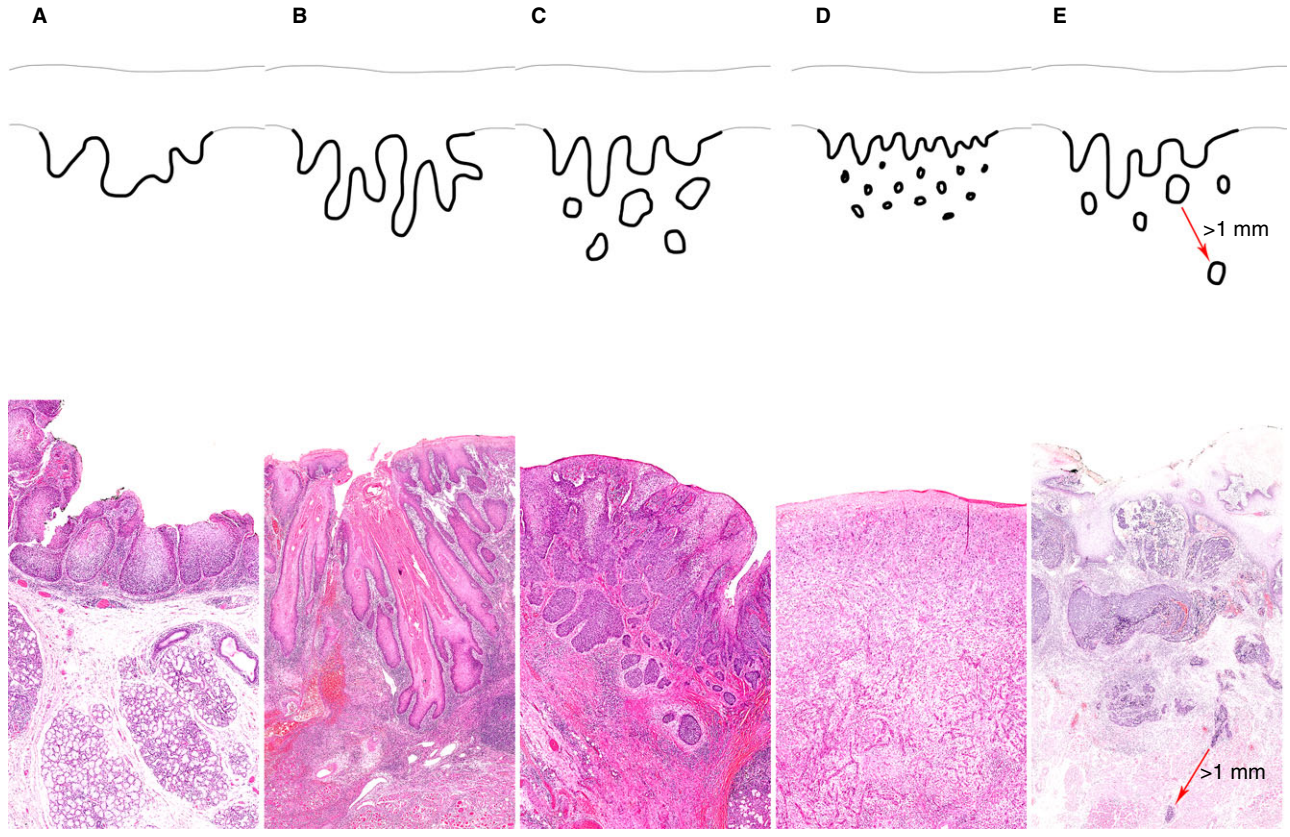

Figure 1. **A**, Pattern of invasion (POI) category 1; pushing well-delineated infiltrating borders. **B**, POI category 2; infiltrating, solid cords, bands and/or strands. **C**, POI category 3; with small groups or cords of infiltrating cells ($n > 15$). **D**, POI category 4; with marked and widespread cellular dissociation in small groups of cells ($n < 15$) and/or in single cells. **E**, POI category 5; with tumour satellites of any size ≥ 1 mm away from main tumour or next closest satellite with intervening normal tissue.

Table 2. Patient and tumour characteristics (n = 211)

	Total population		Neck-treated patients		Watchful-waiting patients		
	N	%	*n*	%	*n*	%	*P*
Patient total	211		173		38		
Age (years)							
Median	61		61		61.5		0.783
Range	25–94		25–94		32–77		
Gender							
Male	118	56	94	54	24	63	0.321
Female	93	44	79	46	14	37	
Tumour localization							
Tongue	108	51	81	47	27	71	
Gum	14	7	11	6	3	8	
Floor of mouth	64	30	63	36	1	3	
Buccal mucosa	7	3	5	3	2	5	
Retromolar area	12	6	9	5	3	8	
Other	6	3	4	2	2	5	
Pathological T-stage							
pT1	122	58	84	49	38	100	
pT2	89	42	89	51	0	0	
Pathological N-stage							
pN0	101	48	101	58	0	0	
pN+	72	34	72	42	0	0	
pNx	38	18	0	0	38	100	
Invasion depth (mm)							
Median	6		6.5		3.2		
Range	0.1–20.0		0.1–20.0		0.8–9.0		
Perineural growth							
Absent	176	83	140	81	36	95	
Present	35	17	33	19	2	5	
Lymph-/angioinvasion							
Absent	192	91	154	89	38	100	
Present	19	9	19	11	0	0	
Resection margin							
Tumour free	143	68	111	64	32	84	
Marginally free	36	17	31	18	5	13	
Tumour positive	32	15	31	18	1	3	

Table 2. *(Continued)*

	Total population		Neck-treated patients		Watchful-waiting patients		
	N	%	*n*	%	*n*	%	*P*
Lymph node dissection							
Yes	173	82	173	100	0	0	
No	38	18	0	0	38	100	
Radiation therapy							
Yes	72	34	72	42	0	0	
No	139	66	101	58	38	100	
Chemotherapy							
Yes	1	0.5	1	1	0	0	
No	210	99.5	172	99	38	100	

see Table 1B and Figure 1.[4,5,8,10,12,13,16,17,21] Subsequently, sum scores were calculated for both PPOI/SPPOI and PPOI/WPOI. To score the invasive tumour front according to the current standard of scoring in two categories, we considered the POI as non-cohesive when > 20% of the invasive tumour front showed marked and widespread cellular dissociation in small groups of cells ($n < 15$) and/or in single cells.[3,22]

SCORING PROCEDURE

Ten cases were chosen randomly and used to achieve consensus on the aforementioned histological criteria between both observers. Subsequently, all cases were scored in chronological order by a well-trained pathology resident (M.G.J.H.). To assess the interobserver reproducibility of the different scoring systems, all cases were also scored in random order by an experienced head–neck pathologist (B.v.d.V.), who was blinded from the scores of the other observer. Randomization was performed by an independent person from the department of Epidemiology at the University Medical Center Groningen.

STATISTICAL ANALYSIS

The interobserver variability of the different scoring systems was analysed using Cohen's kappa.[25] For this analysis, both the four-tiered categories and the sum scores were separated into two categories, both at different levels.

To assess the added value of the different scoring methods compared to the common predictors of outcome measures (LRRFS and DSS), univariate and multivariate Cox regression analyses were performed. In addition, Harrell's C statistics were calculated. This is a method to quantify the added value of the different scoring methods to the common predictors.[26]

Statistical analysis was performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Harrell's C statistics were calculated using Stata version 11.2 (StataCorp, College Station, TX, USA). For all statistical procedures, the level of statistical significance was set at 5% ($P < 0.05$).

Results

STUDY POPULATION

Patient and tumour characteristics are shown in Table 2. A neck dissection was performed in 173 patients (82%), 101 of whom were pN0 (58%) and 72 were pN+ (42%). Of the 105 pathological T1 and clinically N0 patients, watchful-waiting was performed in 38 (36%). There was no significant difference in age and gender between the patients treated by neck dissection and patients in the watchful-waiting group. The median follow-up was 64 months (range 0–193 months).

INTEROBSERVER AGREEMENT

The kappa scores of the POI ranged from 0.292 to 0.454 for the raw data (Table 3). The reproducibility improved by recategorizing the scores into two categories, but was never better than moderate. The PPOI was best reproducible when separated between

Table 3. Interobserver concordance using Cohen's kappa

	Cohen's kappa (95% CI)
Growth pattern whole tumour in 4 categories (n = 211)	0.409 (0.297–0.521)
Growth pattern whole tumour categories 1 and 2 versus 3 and 4	0.439 (0.317–0.561)
Growth pattern whole tumour categories 1, 2 and 3 versus 4	0.395 (0.157–0.947)
Tumour front cohesive versus non-cohesive (n = 211)	**0.557 (0.441–0.673)**
PPOI in 4 categories (n = 211)	0.454 (0.350–0.558)
PPOI categories 1 and 2 versus 3 and 4 (n = 211)	**0.522 (0.404–0.640)**
PPOI categories 1, 2 and 3 versus 4 (n = 211)	**0.580 (0.392–0.768)**
Summed PPOI and SPPOI (n = 211)	0.318 (0.234–0.402)
Summed PPOI and SPPOI; sum score 2–6 versus 7–8 (n = 211)	**0.528 (0.408–0.648)**
WPOI 4 categories (n = 211)	0.346 (0.240–0.452)
WPOI categories 1 and 2 versus 3 and 4 (n = 211)	0.400 (0.198–0.602)
WPOI categories 1, 2 and 3 versus 4 (n = 211)	0.455 (0.337–0.573
Summed PPOI and WPOI (n = 211)	0.292 (0.208–0.376)
Summed PPOI and WPOI; sum score 2–6 versus 7–8 (n = 211)	**0.573 (0.461–0.685)**
Summed PPOI and WPOI; sum score 2–5 versus 6–8 (n = 211)	0.479 (0.357–0.601)
WPOI 5 categories (n = 211)	0.319 (0.221–0.417)

PPOI, predominant pattern of invasion; SPPOI, second most predominant pattern of invasion; WPOI, worst pattern of invasion; CI, confidence interval.
Concordances of > 0.5 (moderate or better) are shown in bold type.

categories 1, 2 and 3 versus 4 ($\kappa = 0.580$). When separating PPOI between categories 1 and 2 versus 3 and 4 the kappa value decreased to 0.522. Other moderately reproducible scoring categories were the summed PPOI and SPPOI separated between a sum score of 2–6 versus 7–8 ($\kappa = 0.528$) and the summed PPOI and WPOI separated between a sum score of 2–6 versus 7–8 ($\kappa = 0.573$). The current standard of scoring in cohesive and non-cohesive POI showed a kappa value of 0.557.

UNIVARIATE SURVIVAL ANALYSIS

In univariate analysis, all the commonly used prognostic histopathological parameters showed a statistically significant association with LRRFS and DSS, with the exception of resection margin status (Table 4).

Univariate Cox regression analysis showed a significant association with LRRFS and DSS for four of the five moderately reproducible methods of POI scoring (see Table 5). Only PPOI categories 1, 2 and 3 versus 4 did not show a significant association with survival.

MULTIVARIATE SURVIVAL ANALYSIS AND ANALYSIS OF THE ADDED VALUE OF INVASIVE FRONT GRADING

The results of the multivariate analysis for commonly used prognostic factors are shown in Table 4. The pathological N-stage is the most predictive independent variable. Perineural growth is associated significantly with death of disease. No significant associations for resection margin status were found in the multivariate analyses. The Harrell's C index for the currently used prognostic histopathological variables pathological N-stage, perineural growth and resection margin status was 0.66 for LRRFS and 0.67 for DSS (Table 4).

The results of the multivariate analysis for the different POI scoring methods are shown in Table 5. The currently used scoring of cohesive versus non-cohesive pattern of invasion (defined as PPOI and/or SPPOI as category 4) showed no significant association with LRRFS or DSS. However, when separating cohesive versus non-cohesive growth using the PPOI (separated between categories 1 and 2 versus 3 and 4) a significant association was found with both LRRFS and DSS. Comparable statistically significant associations were also found for the summed PPOI and WPOI when dividing the groups at a sum score of ≤ 6 or ≥ 7.

When adding the invasive tumour front scoring to the currently used prognostic histopathological variables, the Harrell's *C* index improved only marginally to a maximum of 0.69 for LRRFS and 0.73 for DSS (Table 5). The variance in Harrell's *C* index between the different ways of scoring the invasive tumour pattern is also small: 0.67–0.69 for LRRFS and 0.70–0.73 for DSS.

Table 4. Survival analysis of LRRFS and DSS for commonly used histological parameters

		LRRFS HR (95% CI)	*P*	DSS HR (95% CI)	*P*
Pathological N-stage					
pN0		1		1	
pN+	Univariate HR	4.096 (1.957–8.574)	0.000	5.229 (2.457–11.130)	0.000
	Adjusted HR[a]	3.837 (1.771–8.314)	0.001	4.205 (1.893–9.342)	0.000
pNx	Univariate HR	2.349 (0.954–5.782)	0.063	1.081 (0.333–3.512)	0.897
	Adjusted HR[a]	2.328 (0.945–5.738)	0.066	1.107 (0.340–3.602)	0.866
Perineural growth					
No		1		1	
Yes	Univariate HR	2.441 (1.252–4.758)	0.009	3.777 (1.989–7.171)	0.000
	Adjusted HR[a]	1.873 (0.912–3.844)	0.087	2.233 (1.117–4.463)	0.023
Resection margin					
Free/marginally free		1		1	
Tumour positive	Univariate HR	1.152 (0.513–2.589)	0.732	2.076 (1.014–4.247)	0.046
	Adjusted HR[a]	0.708 (0.297–1.686)	0.435	0.991 (0.463–2.121)	0.981
Harrell's C					
LRRFS	0.6608				
DSS	0.6707				

LRRFS, locoregional recurrence-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval.
[a]Adjusted for the other variables in this table in multivariate Cox analysis.

Discussion

In this study, the prognostic value and interobserver reproducibility of several methods of POI scoring in oral squamous cell carcinoma were evaluated. The additional prognostic value of POI scoring was also analysed. POI showed moderate reproducibility for five different methods of scoring. Of these five methods, the PPOI and the summed PPOI and WPOI were independent prognosticators for LRRFS and DSS. The currently used cohesive versus non-cohesive POI was reproducible, but it showed no significant correlation with LRRFS or DSS in multivariate analysis. Compared with the currently used prognostic histopathological parameters, invasive tumour front scoring had little additional value when using either the PPOI or the summed PPOI and WPOI.

The kappa scores of the different scoring methods for POI ranged from 0.292 to 0.580. Five of the scoring systems had a moderate kappa, which is comparable with previous literature: Sawair *et al.* showed an interobserver reproducibility with a kappa value of 0.193 for POI, when categorized into four categories. The kappa value improved to 0.449 when the POI was reclassified into two categories.[4] Chang *et al.* showed a kappa score of 0.69 for interobserver agreement for the original sum score of PPOI and SPPOI, which improved to 0.72 when reclassified into two categories (sum score of ≤ 4 or ≥ 5).[14] A major difference with our study is that they used OSCC of all T-stages, contrary to our low-stage group. Their higher level of agreement can be explained because invasion patterns are more divergent between low- and high-stage carcinomas. Moreover, their cut-off for classifying patients in a low and high category is significantly lower than our cut-off (sum score of ≤ 4 versus a sum score of ≤ 6). More than moderate agreement has not been reached by any of the previous studies and might be (almost) impossible, because no matter how sharply defined the categories, it remains a subjective judgement of an individual pathologist. When looking at the percentages of agreed cases, this varied between 76 and 93% for the five methods of POI scoring. For the PPOI, 50 cases were not concordant when separating the groups

Table 5. Survival analysis of LRRFS and DSS for different pattern of invasion scoring systems

		LRRFS HR (95% CI)	*P*	DSS HR (95% CI)	*P*
Tumour front cohesive/non-cohesive (*n* = 211)					
Cohesive		1		1	
Non-cohesive	Univariate HR	1.923 (1.055–3.503)	0.033	2.259 (1.206–4.230)	0.011
	Adjusted HR[a]	1.827 (0.963–3.467)	0.065	1.729 (0.874–3.419)	0.116
	Harrell's C	0.6750		0.7115	
PPOI patterns 1 and 2 versus patterns 3 and 4 (*n* = 211)					
Patterns 1 and 2		1		1	
Patterns 3 and 4	Univariate HR	2.458 (1.281–4.716)	0.007	3.125 (1.527–6.397)	0.002
	Adjusted HR[a]	2.095 (1.062–4.134)	0.033	2.290 (1.075–4.878)	0.032
	Harrell's C	0.6901		0.7272	
PPOI patterns 1, 2 and 3 versus pattern 4 (*n* = 211)					
Patterns 1, 2 and 3		1		1	
Pattern 4	Univariate HR	1.497 (0.535–4.191)	0.443	2.172 (0.850–5.549)	0.105
	Adjusted HR[a]	1.194 (0.408–3.498)	0.746	1.516 (0.564–4.076)	0.410
	Harrell's C	0.6729		0.6955	
Summed PPOI/SPPOI; sum scores 2–6 versus 7–8 (*n* = 211)					
Sum score 2–6		1		1	
Sum score 7–8	Univariate HR	2.022 (1.110–3.685)	0.021	2.375 (1.268–4.448)	0.007
	Adjusted HR[a]	1.890 (0.996–3.585)	0.051	1.790 (0.904–3.542)	0.095
	Harrell's C	0.6747		0.7153	
Summed PPOI and WPOI; sum scores 2–6 versus 7–8 (*n* = 211)					
Sum score 2–6		1		1	
Sum score 7–8	Univariate HR	2.386 (1.284–4.432)	0.006	2.931 (1.511–5.686)	0.001
	Adjusted HR[a]	2.158 (1.106–4.213)	0.024	2.123 (1.022–4.412)	0.044
	Harrell's C	0.6912		0.7284	

LRRFS, locoregional recurrence-free survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; PPOI, predominant pattern of invasion; SPPOI, second most predominant pattern of invasion; WPOI, worst pattern of invasion.
[a]Adjusted for pathological N-stage, perineural growth and resection margin status.

between categories 2 and 3; this improved to only 16 non-concordant cases when separating the categories between categories 3 and 4. This suggests that the fourth category is easier to recognize. Unfortunately, in multivariate analyses only the combination of the third and fourth category gives a significant adverse prognosis. Therefore, when using only the fourth category as an indicator of worse prognosis, a significant number of patients at risk for locoregional recurrence and disease-specific death are disregarded, even though they might benefit from postoperative radiotherapy. The fifth category, as defined by Brandwein-Gensler *et al.*, was seen only rarely and always constituted a minority of the invasive tumour front (< 20%). Therefore, we only evaluated this item as a WPOI.[8,10,13] With a kappa value of 0.319 for inter-observer agreement, this scoring method was considered too unreliable for use in clinical practice, so it was excluded from further statistical analysis. Chang *et al.* also excluded this fifth pattern from their study

because they considered it too infrequent, unpredictable and unmeasurable.[14]

According to Dutch guidelines, a non-cohesive growth pattern is a minor criterion for postoperative radiotherapy.[3] In our study a non-cohesive POI was moderately reproducible (kappa = 0.557); however, in multivariate analysis it did not show a significant association with either LRRFS or DSS. PPOI, when recategorized into two categories, showed a significant correlation with both LRRFS and DSS, even when corrected for pathological N-stage, perineural growth and resection margin status. Comparable hazard ratios and significance were found when using a sum score of PPOI and WPOI (sum score of 2–6 versus 7–8). However, the current definition of non-cohesive growth is not defined clearly, and therefore the cut-off for calling a tumour non-cohesive might have to be adjusted; for instance, by using the definitions of PPOI, with a cut-off for non-cohesive growth between categories 2 and 3. This would mean that patients with a PPOI in small groups or cords of infiltrating cells and/or in single cells could benefit from postoperative radiotherapy. With more clearly defined definitions and with future experience using these criteria the reproducibility between pathologists might even improve. Intraobserver variation is not addressed in the current study, and should be assessed in further studies.

To our knowledge, this is the first study to assess the value of POI scoring in addition to the commonly used histopathological markers. Our finding that this additional value is low can therefore not be confirmed in literature. This should be a subject of future research.

In conclusion, this study confirms that POI is an independent prognosticator for LRRFS and DSS in low-stage OSCC. PPOI or the combined score of PPOI and WPOI separated into two categories emerges as the most promising prognostic value. The currently used non-cohesive growth pattern as an indicator for adjuvant radiotherapy shows potential, but a clear definition is missing. According to our results, non-cohesive growth can be best defined as a PPOI in small groups or cords of infiltrating cells and/or in single cells. The value of POI scoring in addition to commonly used histopathological criteria for the prediction of locoregional control and overall survival is limited. POI should therefore remain a minor criterion for postoperative radiotherapy. To evaluate if patients with low-stage oral squamous cell carcinoma and with a non-cohesive POI will actually benefit from postoperative radiotherapy, a prospective randomized controlled trial should be performed.

Acknowledgements

The authors thank Nic J. G. M. Veeger (Clinical Epidemiologist, Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands) for performing the independent randomization.

Conflicts of interest

None to declare.

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