Head and Neck Pathology (2023) 17:479–486
https://doi.org/10.1007/s12105-023-01533-1

ORIGINAL PAPER

WPOI-5: Accurately Identified at Intraoperative Consultation and Predictive of Occult Cervical Metastases

John E. Beute[1] · Lily A. Greenberg[1] · Lauren E. Wein[1] · Danielle A. Kapustin[1,2] · Jun Fan[3] · Eric M. Dowling[2] · Shabnam Samankan[4] · Ammar Matloob[3] · Monica Xing[1] · Ippolito Modica[3] · Daniel Chung[3] · William Carroll[5] · Eben L. Rosenthal[5,6] · Mohemmed Nazir Khan[2] · Raymond L. Chai[2] · Margaret S. Brandwein-Weber[3] · Mark L. Urken[1,2]

Received: 26 October 2022 / Accepted: 12 January 2023 / Published online: 28 February 2023

Abstract

Background Frozen section analysis of oral cancer specimens is ideal for assessing margin distances and depth of invasion (DOI); the latter impacts intraoperative decisions regarding elective neck dissection (END). Here, we show that intraoperative determination of worst pattern of invasion (WPOI), specifically WPOI-5, has a high level of accuracy. This relates to our demonstration herein that WPOI-5 predicts occult cervical metastases (OCM) for pT1 oral squamous carcinoma (OSC).

Methods The presence of OCM was correlated with WPOI in 228 patients with primary T1/T2/cN0 OSC undergoing resection and END. Concordance between intraoperative and final pathology WPOI determination was assessed on 51 cases of OSC.

Results WPOI-5 predicts OCM in pT1 patients, compared with WPOI-4/WPOI-3 ($p < 0.0001$). Most pT1 WPOI-5 tumors had DOI of 4–5 mm (24/59 or 40.7%). Only two pT1 WPOI-5 tumors had DOI < 4 mm (3.0 and 3.5 mm). If END were performed in this pT1 cohort for all WPOI-5 OSC patients regardless of DOI, *OR* all OSC patients with DOI ≥ 4 mm regardless of WPOI, then no OCM would be missed ($p = 0.017$, 100% sensitivity, 29% specificity, 77% positive predictive value, 23% negative predictive value). With respect to intraoperative WPOI-5 determination, the accuracy, sensitivity, and specificity was 92.16, 73.33, and 100.0%, respectively.

Conclusions DOI ≥ 4 mm is the dominant predictor of OCM. For the rare WPOI-5 OSC with DOI < 4 mm, it is reasonable to suggest that surgeons perform END. WPOI-5 may be accurately determined intraoperatively. As microscopic instruction is needed to accurately assess WPOI-5, a teaching link is included in this manuscript.

Keywords Frozen section pathology · Permanent section pathology · Oral cavity squamous cell carcinoma · Worst pattern of invasion · Cervical occult metastases

✉ Danielle A. Kapustin
danielle.kapustin@thancfoundation.org

[1] Thyroid, Head and Neck Cancer (THANC) Foundation, 10 Union Square East, Suite 5B, New York, NY 10003, USA

[2] Department of Otolaryngology-Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, 10 Union Square East, Suite 5B, New York, NY 10003, USA

[3] Department of Pathology, Icahn School of Medicine at Mount Sinai, 1468 Madison Avenue, New York, NY 10029, USA

[4] Department of Pathology, George Washington University, 2300 M Street NW, 7Th Floor, Washington, DC 20037, USA

[5] Department of Head and Neck Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

[6] Department of Otolaryngology–Head and Neck Surgery, Vanderbilt University Medical Center, 1215 21St Avenue South Suite 6310, Medical Center East – South Tower, Nashville, TN 37232-8605, USA

Introduction

Brandwein et al. proposed the worst pattern of invasion (WPOI) as a histologic variable in 2005 [1]. It has since been validated as a prognosticator in oral squamous carcinoma (OSC) [1–13]. The histologic risk model incorporated a new class of WPOI known as WPOI-5, which portends significantly poorer outcomes in OSC patients as compared to WPOI-4 [1].

Currently, WPOI-5 is an American Joint Committee on Cancer (AJCC) 8th edition registry data collection variable and a reporting element in the College of American Pathologists (CAP) synoptic for oral cancers [14, 15]. Previous studies have established that WPOI-5 is significantly predictive of locoregional recurrence (LRR) and disease specific survival (DSS) [3]. Thus, the ability to accurately identify WPOI-5 intraoperatively has implications for real-time surgical decision-making. Kohler et al. demonstrate that WPOI affects the extent of tumor resection since more aggressive tumors (WPOI-4 and WPOI-5) require more extensive margins to minimize risk of LRR [16]. WPOI-5 has significant implications for the management of regional lymph nodes as well. The objectives of this study are to determine the following: (1) The association of WPOI-5 with occult cervical metastases (OCM), and (2) The accuracy of WPOI-5 identification at frozen section analysis. Additionally, a link to a teaching module on the recognition of WPOI-5 is included in this manuscript.

Materials and Methods

Retrospective Study

The Institutional Review Board approved the study of OSC patients who were clinically/radiologically cN_0 and who underwent primary resection and elective neck dissection (END). The data collected included 8th edition AJCC T and N stage, depth of invasion (DOI), WPOI, size of positive lymph nodes, perineural invasion (PNI), and extranodal extension (ENE). All cases were originally diagnosed by MBW and then re-reviewed for this study. DOI was measured either using a digital pathology platform or, for pre-digital cases, by overlaying the glass slides with an acetate-printed millimeter ruler. The DOI was measured from the estimated position of basal reserve cells to the furthest invading tumor islands. Data were stored in a secure database. Sensitivity, specificity, and predictive values tests were performed online using the MedCalc© diagnostic test evaluation calculator (MedCalc Software Ltd. 2022).

Prospective Study

Following Institutional Review Board approval, 47 patients undergoing 51 surgeries were enrolled over 30 months from a single institution (Mount Sinai West Hospital, New York, NY). Informed consent was obtained from each patient. All patients underwent standard of care surgery for biopsy-proven OSC—either primary resection ($n=47$) or salvage resection ($n=4$). Concordance between intraoperative and final pathology WPOI classification was examined. WPOI was determined as part of routine resection margin assessment as follows: T1 and T2 carcinomas are examined in entirety and T3/T4 tumors are examined generously at the time of frozen section during margin assessment. Clinicopathologic information (surgical procedure, frozen WPOI, final WPOI, and pathological T-stage) were recorded and stored in a secure database on the internal Mount Sinai Hospital network. The frozen section WPOI data were collected either from (1) an intraoperative frozen section WPOI determination recorded in real-time by a single pathologist with expertise in head and neck pathology or based on (2) hematoxylin and eosin frozen section slides reviewed *ex post facto* by the same pathologist, blinded to permanent section results. WPOI was classified as either non-aggressive (WPOI 1–3), WPOI-4, or WPOI-5. Final WPOI from permanent section was retrieved from Dr. Brandwein-Weber's pathology reports. Each frozen WPOI was compared with the corresponding final WPOI. Since the variable of interest in the current study is WPOI-5, for purposes of assessing accuracy, WPOI-4 was lumped together with non-aggressive patterns of invasion. Sensitivity, specificity, and predictive value tests were performed online using the MedCalc© diagnostic test evaluation calculator (MedCalc Software Ltd. 2022).

Results

The retrospective study was comprised of 228 patients with pT1/pT2 cN0 OCM (staged by AJCC 8th edition) who underwent primary resection and END. Thirteen pT1 patients had occult cervical metastases; 10 with WPOI-5, 2 with WPOI-4, and 1 with WPOI-3 (Table 1). The majority of pT1 WPOI-5 carcinomas (24/26) had DOI ≥ 4 mm, with most occurring between 4 and 5 mm (Table 2). Only two pT1 WPOI-5 carcinomas had DOI < 4 mm (3.0 and 3.5 mm), and both patients had OCM. PNI data is known for 20/26 pT1 patients with OCM. This includes only one of the two pT1 cases with both WPOI-5 and DOI < 4 mm. PNI was present in two of 20 cases; the aforementioned

Table 1 Occult metastases for pT1/pT2 cN0 by WPOI ($N=228$) (%)

		WPOI-5 (%)	WPOI-4 / WPOI-3 (%)	*p*
pT1	pN0 63 (79.7)	13 (50)	50 (94.3)	< 0.0001
	pN + 16 (20.3)	13 (50)	3 (5.7)*	
	Total 79 (100)	26 (100)	53 (100)	
pT2	pN0 116 (77.9)	25 (71.4)	91 (79.8)	NS
	pN + 33 (22.1)	10 (28.6)	23 (20.2)	
	Total 149 (100)	35 (100)	114 (100)	

*These were: WPOI-3, DOI 5 mm; WPOI-4, DOI 4.1 mm; and WPOI-4, DOI 5 mm

Table 2 Distribution of occult metastases for pT1 by depth of invasion (DOI) (%)

	WPOI-5 (%)	pN +
pT1 DOI < 4 mm (N = 20)	2 (10.0)	2 (10.0)
pT1 DOI ≥ 4 mm (N = 59)	24 (40.7)	11 (18.6)

case with both WPOI-5 and DOI < 4 mm was negative for PNI.

WPOI-5 was significantly predictive of OCM in 26 of 79 pT1 patients as compared to WPOI-4/WPOI-3 ($p < 0.0001$) (Table 1). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of predicting OCM in pT1 patients were 50%, 94.3%, 81.3%, 79.4% and 81.1%, respectively.

If all pT1 pN0 patients are treated with END, the expected overtreatment rate is 80%. This rate can be reduced to approximately 50% if only patients with pT1 *AND* WPOI-5 disease received END. However, in doing so, OCM would be missed in 4% of patients (pT1 pN + WPOI-4 / WPOI-3). If END were performed in our cohort for all pT1 ≥ 4 mm (regardless of WPOI) or all WPOI-5 (regardless of DOI), then no OCM would have been missed ($p = 0.017$, 100% sensitivity, 29% specificity, 77% positive predictive value, 23% negative predictive value).

In the prospective study of the 51 tumor samples (Table 3), 15 were WPOI-5, 15 were WPOI-4, and 21 were non-aggressive (WPOI 1-3) on final pathology (Table 4). Intraoperative consultation correctly assigned WPOI in 42 of 51 cases (82.4%). Eleven pairs were classified as "true positive," meaning the diagnosis of WPOI-5 was rendered on both frozen and permanent sections. Thirty-six pairs were considered "true negative," meaning the tumor was not classified as WPOI-5 on frozen or permanent section.

Four pairs were classified as "false negative," meaning the tumor was reclassified to WPOI-5 on permanent section after being classified as non-aggressive or WPOI-4 on frozen section. There were no false positives. We tested the hypothesis that this discrepancy, which is related to sampling error, correlates with increased tumor size (pT1/pT2 vs pT3/pT4 or recurrent tumor ≥ 4 cm). We found a trend ($p = 0.059$) which supports this hypothesis (Fisher' exact test, one-tailed).

With respect to identifying WPOI-5, the accuracy, sensitivity, and specificity were 92.16%, 73.33%, and 100.0%,

Table 3 Prospective cohort: 47 patients with 51 resections

Age range	32–95
Males	23
Females	24
Primary resections	42
T1	12
T2	9
T3	8
T4	13
Salvage resections	9
Tumor size range	0.5–5.8 cm
Anatomic subsite	
Tongue	28
Gingiva	8
Buccal	6
Palate	3
Retromolar trigone	2
Maxilla	2
Lip	1
Floor of mouth	1

Table 4 WPOI concordance between intraoperative/permanent section ($N=51$, $p=0.017$)

	Frozen WPOI	Permanent WPOI
Non-aggressive (WPOI 1-3) (%)	25 (49)	21 (42)
WPOI-4 (%)	15 (29)	15 (29)
WPOI-5 (%)	11 (22)	15 (29)

Table 5 WPOI-5 identification during intraoperative consultation compared to final pathology results

Statistic	Value	95% CI
Sensitivity	73.33%	44.90–92.21%
Specificity	100.00%	90.26–100.00%
Negative Likelihood Ratio	0.27	0.12–0.62
Disease prevalence	29.41%	17.49–43.83%
Positive Predictive Value	100.00%	
Negative Predictive Value	90.00%	79.54–95.42%
Accuracy	92.16%	81.12–97.82%

respectively (Table 5). The most common discrepancy was between non-aggressive on frozen and WPOI-4 on permanent ($n=4$). This was followed by WPOI-4 on frozen to WPOI-5 on permanent ($n=3$). All these discrepancies were due to sampling issues. There was one case of non-aggressive on frozen reclassified to WPOI-5 on permanent (sampling error) and one case of WPOI-4 on frozen reclassified to non-aggressive on permanent (interpretive error).

Discussion

WPOI was proposed as a prognosticator in OSC by Brandwein et al. in 2005 [1], validated internally [2, 3] and by numerous external international groups [4–13]. WPOI is categorized as WPOI-1 through WPOI-5. Tumors identified as WPOI-1, WPOI-2, or WPOI-3 are all considered "non-aggressive patterns of invasion," whereas WPOI-4 and WPOI-5 are considered "aggressive patterns of invasion." Generally, tumors with non-aggressive pattern of invasion do not extend beyond their perimeter. WPOI-1 is defined as a pushing border, WPOI-2 is defined as finger-like growth, and WPOI-3 is defined as large separate islands, attached or detached but confined within the tumor perimeter, with more than 15 cells per island. Tumors with aggressive pattern of invasion demonstrate convincingly discontiguous cancer satellites. WPOI-4 is defined as small tumor islands, separated from the main tumor mass, with 15 or fewer cells per island. Carcinomas are categorized as WPOI-5 if their satellites are dispersed (≥ 1 mm away from the main mass or neighboring satellites). The 8th edition of the *AJCC Staging Manual: Oral Cavity* includes WPOI-5 as a recommended reported feature, as this variable is significantly predictive of poorer outcomes [14]. While the most common tumor dispersion phenotype is spread through soft tissue, dispersion may also be the result of extratumoral PNI or lymphovascular tumor emboli in more rare instances [3, 17]. WPOI-5 demonstrates a positive predictive value of 42% for LRR and is significantly predictive of DSS on multivariate analysis when adjusted for confounders [3]. Given the predictive nature of WPOI-5 for disease progression and survival outcomes, this variable can be a useful tool to inform clinical decision-making.

Intraoperative consultation during head and neck resections is the standard of care with respect to margin assessment. Several studies specifically analyzed the consistency between frozen section and permanent section margin analysis. Layfield et al. analyzed 1796 corresponding pairs of frozen and permanent sections to determine the accuracy of intraoperative margins for primary head and neck squamous carcinomas [18]. Concordance was 97%, and discrepancies were identified in only 55 pairs. These discrepancies were predominantly false negatives, in that the frozen section was negative and the permanent section was positive or close [18]. Similar yet smaller studies concur that frozen section is a highly accurate method for clearing tumor margins intraoperatively [19–23]. These studies also shed light on the limitations associated with frozen sections [20–25]. One limitation is the unusual event of positive margins in the final report which were not detected during frozen tissue analysis [23]. Possible sources of sampling errors may come from either undetected tumor in deeper sections within the frozen tissue block or from sampling additional tissues for permanent sections. Serinelli et al. analyzed whether sampling additional deeper levels from the frozen section blocks improves concordance [26]. They compared 654 tissue blocks: 532 had two slides cut during frozen section and 122 blocks had ≥ 3 slides cut. They found no significant difference in concordance, suggesting that examination of deeper frozen sections might not reduce discordance [26]. Sampling the entire specimen in pT1 and pT2 OSC obviates the possibility of tissue sampling discordance.

This is the first study to demonstrate that WPOI-5 can be accurately identified intraoperatively (92.2%). The specificity of identifying WPOI-5 on frozen section was 100%. In other words, no cases were misassigned as WPOI-5 on frozen section. This is meaningful as it prevents unnecessarily aggressive surgical management. Four cases were identified as WPOI-5 only on permanent section (false negative) due to sampling errors, which is an expected limitation of intraoperative assessment.

If the patient's tumor is identified as WPOI-5 only at permanent section, the patient can return to the operating room for more surgery, if required. On the other hand, more aggressive surgery (e.g., wider resection of the tumor, END) should be considered if WPOI-5 is identified on frozen section [16] since WPOI-5 is associated with inadequate resection margins [1]. Importantly, Kohler and colleagues have recently confirmed that optimal margin distance is influenced by WPOI in a large retrospective study of 772 intraoral cancer patients. They demonstrated that the optimal resection margin distance for tumors with non-aggressive WPOI was 1.7 mm, whereas the optimal distance for grouped WPOI-4/WPOI-5 tumors was 7.8 mm [16]. While our current standards of care will not be changed solely based on conclusions drawn from retrospective studies, their study should serve as the basis for prospective study designs that will arrive at new treatment recommendations.

A potential study limitation is that three frozen section cases were reviewed *ex post facto.* However, given the time lapse ("wash out" period) between signing out the permanent section results and reviewing the frozen slides while blinded to the final report, this did not influence study results.

Beyond resection margin distances, depth of invasion (DOI) is another important feature that can be determined during surgery, as it predicts occult cervical metastases

(OCM) and influences decisions regarding END. The accuracy of intraoperative DOI is 96.8%, confirming its reliability as a frozen section parameter [27]. Van Lanschot and colleagues investigated the optimal cut-off value for indicating END in early-stage oral cavity SCC ($n=300$) and report that DOI ≥ 4 mm was appropriate for END [28]. Some of the debate regarding the optimal DOI cut point may be caused by inaccurately considering tumor thickness (TT) and DOI as synonymous [29, 30]. When accurate and distinct definitions are utilized for these two prognostic features, only DOI accounts for exophytic and ulcerative tumors, which strengthens its value as a prognostic factor [30]. Multiple reports have supported a cut-off value of 4 ± 0.5 mm [29–31].

Other groups have also looked at WPOI-5 in the context of OCM. Verma et al. demonstrated that WPOI-5 was predictive of OCM ($p=0.0213$) for a combined group of 189 pT1/pT2 patients but did not stratify for DOI [32]. Larson and colleagues were unable to demonstrate an association between WPOI-5 and occult cervical metastasis in a smaller group of pT1-T2/cN0 patients undergoing END [33]. This small cohort size of 35 pT1/cN0 patients included only one patient with OCM (personal communication). Shan and colleagues identified only one WPOI-5 tumor in a cohort of 145 OCM patients, casting doubt on their assessment [34]. Shimizu and colleagues studied 91 patients with clinically low-stage oral cancer; 75% of cancers were < 4 mm. Only 12 patients (13%) underwent END and only three patients (3.2%) had occult cervical metastasis [8]. Therefore, this study was not optimally designed to address predictors of OCM.

The current study is the first demonstration that WPOI-5 significantly predicts OCM for pT1 OSC. Thirteen pT1 patients had occult cervical metastases; 10 with WPOI-5, 2 with WPOI-4, and 1 with WPOI-3 (Table 1). Most pT1 WPOI-5 carcinomas are clustered at a DOI between 4 and 5 mm, thus these patients would have received END based on DOI. The three WPOI-3/WPOI-4 patients with OCM would also have received END based on DOI (Table 1). However, two patients with WPOI-5 had DOI < 4 mm, and both demonstrated OCM. As significance was lost for pT2 patients, we conclude that DOI > 5 mm is the dominant OCM predictor. If END were performed in our cohort for all pT1 ≥ 4 mm (regardless of WPOI) or all WPOI-5 (regardless of DOI), then no OCM would have been missed ($p=0.017$, 100% sensitivity, 29% specificity, 77% positive predictive value, 23% negative predictive value). DOI ≥ 4 mm is the dominant determinant of OCM in this cohort. We would like to stress that WPOI-5 tumors with DOI < 4 mm are extremely rare. However, it is reasonable to suggest, based on these data, that END be performed for Stage I OSC with DOI < 4 mm and WPOI-5.

Our study assures that classifying WPOI both on frozen and permanent sections use the same approach as proposed by Brandwein-Gensler et al. [1]. For example, in both instances, if there are no satellites convincingly separate from the main tumor, then this is a non-aggressive pattern of invasion. If one sees separate tumor satellites at the advancing edge that are large (> 15 cells), this too represents non-aggressive pattern of invasion. If the separate tumor satellites at the advancing edge are small (≤ 15 cells), then the tumor is classified as WPOI-4. Tumor dispersion, characteristic of WPOI-5, can usually be appreciated at low-power as satellites are interspersed with sizable regions of normal soft tissue. The size of the satellites become immaterial. Dispersion is measured either between a satellite and the closest point within the main tumor, or between waves of satellites. A dispersion distance of at least 1 mm represents WPOI-5. We emphasize that, irrespective of frozen or permanent setting, having knowledge and experience with WPOI classification is essential for accurate risk stratification and prediction of OCM, as we demonstrate here.

The art of pathology, just like the art of surgery, has always been passed from teacher to student by experiential one-on-one teaching, akin to apprenticeship, be it at the multi-headed microscope, a computer screen, or at the operating room table [35, 36]. Samulski et al. emphasized the challenges associated with teaching and learning a predominantly visual-based field, such as pathology [35]. Assessing risk score and recognizing WPOI-5 are perfect examples within pathology that require experiential learning. We demonstrated substantial interrater agreement [$\kappa=0.64$, 95% CI (0.46–0.79)] as well as substantial agreement between raters and the standard [$\kappa=0.87$, 95% CI (0.69–1.00)] for risk classification [2]. Even with such high concordance, agreement was substantially improved after lecture participation, review of printed materials, and a multi-headed microscope teaching session, as compared with risk scoring after only reading published criteria (data not shown). Chang and colleagues expressed doubt regarding the reproducibility of WPOI-5 [37]. Heerema and colleagues investigated the reproducibility of pattern of invasion scoring and found no more than moderate interobserver agreement [38]. In this study, a significant limitation is the lack of comparison between their reads and the gold standard. Such suboptimal performance reflects inherent learning limitations when the experiential component is lacking. We have previously cautioned, "*Surgical pathologists at other institutions who would like to use the Risk Model should first seek out practical training sessions*" [3]. Within the histologic risk model, the rationale for migrating from high-risk categorization (evaluating three variables with a total of nine possible categories) to WPOI-5 as a single binary variable (yes or no) was to promote the inclusion of WPOI as a recommended feature in 8th AJCC Staging. To further increase adaptation and reproducibility of this prognosticator, we created a teaching

module (YouTube video) to provide an active visual demonstration rather than solely relying on written text.

YouTube Link for WPOI Teaching Module by Dr. Margaret Brandwein-Weber: https://www.youtube.com/watch?v=k2dMAgml1H8

Conclusions

WPOI-5 predicts OCM in pT1 patients, which can impact decisions regarding END. The expected rate of overtreatment is 80% if all pT1 pN0 patients are treated with END. This rate can be reduced to approximately 50% if only patients with pT1 *AND* WPOI-5 disease receive END. However, in doing so, OCM would be missed in 4% of patients (pT1 pN + WPOI-4 / WPOI-3). Typically, DOI ≥ 4 is an indication for the surgeon to proceed with sentinel node or neck dissection. We show that for rare cases of WPOI-5 presenting with DOI < 4 mm, WPOI-5 should override the DOI. In such cases, it is reasonable for the surgeon to proceed with END. Since WPOI-5 is known to predict inadequate resection margins and is associated with a high risk of LRR [1, 17], intraoperative identification of WPOI-5 can have significant implications for the extent of tumor resection.

Author contributions All authors whose names appear on the submission (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This study was not supported by any funding.

Data Availability Data is stored in a secure database at our institution and can be provided upon request.

Code Availability Sensitivity, specificity, and predictive values tests were performed online using the MedCalc© diagnostic test evaluation calculator (MedCalc Software Ltd. 2022, RRID:SCR_015044). Statistical methods employed were performed by an experienced person (Dr. Margaret Brandwein), with authorship (acknowledgement) on the manuscript.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate For the retrospective portion of this study, formal consent is not required. For the prospective portion of this study, informed consent was obtained from all individual participants included in the study.

Consent for Publication For this type of study consent for publication is not required.

Human and Animal Participant The Human Investigation Committee (IRB) of Mount Sinai Hospital approved this study.

This article does not contain any studies with animals performed by any of the authors.

References

1. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML, Wang BY (2005) Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. Am J Surg Pathol 29(2):167–178. https://doi.org/10.1097/01.pas.0000149687.90710.21
2. Brandwein-Gensler M, Smith RV, Hebert T, Nason R, Ramer M, Delacure M, Hirsch D, Myssiorek D, Heller K, Prystowsky M, Schlecht NF, Negassa A, Wang B, Penner C, Theilken A, Broughel D, Schiff B, Owen RP, Smith J, Sarta C (2010) Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. Am J Surg Pathol 34(5):676–688. https://doi.org/10.1097/PAS.0b013e3181d95c37
3. Li Y, Bai S, Carroll W, Dayan D, Dort JC, Heller K, Jour G, Lau H, Penner C, Prystowsky M, Rosenthal E, Schlecht NF, Smith RV, Urken M, Vered M, Wang B, Wenig B, Negassa A, Brandwein-Gensler M (2012) 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. Head Neck Pathol (Totowa, NJ) 7(3):211–223. https://doi.org/10.1007/s12105-012-0412-1
4. Chaturvedi A, Husain N, Misra S, Kumar V, Gupta S, Akhtar N, Lakshmanan M, Garg S, Arora A, Jain K (2019) Validation of the Brandwein Gensler risk model in patients of oral cavity squamous cell carcinoma in North India. Head Neck Pathol (Totowa, NJ) 14(3):616–622. https://doi.org/10.1007/s12105-019-01082-6
5. de Matos FR, Lima EdNdA, Queiroz LMG, da Silveira ÉJD (2012) Analysis of inflammatory infiltrate, perineural invasion, and risk score can indicate concurrent metastasis in squamous cell carcinoma of the tongue. J Oral Maxillofac Surg 70(7):1703–1710. https://doi.org/10.1016/j.joms.2011.08.023
6. Karpathiou G, Monaya A, Forest F, Froudarakis M, Casteillo F, Marc Dumollard J, Prades JM, Peoc'h M (2016) p16 and p53 expression status in head and neck squamous cell carcinoma: a correlation with histological, histoprognostic and clinical parameters. Pathology 48(4):341–348. https://doi.org/10.1016/j.pathol.2016.01.005
7. Nadaf A, Bavle RM, Soumya M, D'Mello S, Kuriakose MA, Govindan S (2016) Analysis of the invasive edge in primary and secondary oral squamous cell carcinoma: An independent prognostic marker: a retrospective study. J Oral Maxillofac Pathol 20(2):239–245. https://doi.org/10.4103/0973-029x.185931
8. Shimizu S, Miyazaki A, Sonoda T, Koike K, Ogi K, Kobayashi J-I, Kaneko T, Igarashi T, Ueda M, Dehari H, Miyakawa A, Hasegawa T, Hiratsuka H (2018) Tumor budding is an independent prognostic marker in early stage oral squamous cell carcinoma: with special reference to the mode of invasion and worst pattern of invasion. PLoS One 13(4):e0195451–e0195451. https://doi.org/10.1371/journal.pone.0195451

9. Sinha P, Mehrad M, Chernock RD, Lewis JS Jr, El-Mofty SK, Wu N, Nussenbaum B, Haughey BH (2015) Histologic and systemic prognosticators for local control and survival in margin-negative transoral laser microsurgery treated oral cavity squamous cell carcinoma. Head Neck 37(1):52–63. https://doi.org/10.1002/hed.23553
10. Szybiak B, Trzeciak P, Golusiński W (2012) Role of extended histological examination in the assessment of local recurrence of tongue and floor of the mouth cancer. Rep Pract Oncol Radiother 17(6):319–323. https://doi.org/10.1016/j.rpor.2012.06.001
11. Szybiak B, Korski K, Golusiński W (2015) Role of extended histological examination in the assessment of local recurrence of the oral cancer. Otolaryngol Pol 69(1):17–21. https://doi.org/10.5604/00306657.1136148
12. Vered M, Dayan D, Dobriyan A, Yahalom R, Shalmon B, Barshack I, Bedrin L, Talmi YP, Taicher S (2010) Oral tongue squamous cell carcinoma: recurrent disease is associated with histopathologic risk score and young age. J Cancer Res Clin Oncol 136(7):1039–1048. https://doi.org/10.1007/s00432-009-0749-3
13. Rahman N, MacNeill M, Wallace W, Conn B (2021) Reframing histological risk assessment of oral squamous cell carcinoma in the era of UICC 8th edition TNM staging. Head NECK Pathol (Totowa, NJ) 15(1):202–211. https://doi.org/10.1007/s12105-020-01201-8
14. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP (2017) The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 67(2):93–99. https://doi.org/10.3322/caac.21388
15. Seethala RR, Weinreb I, Bullock MJ, Carlson DL, Ferris RL, Harrison LB, McHugh JB, Pettus J, Richardson MS, Shah J, Thompson LDR, Wenig BM. Protocol for the examination of specimens from patients with cancers of the oral cavity. http://www.cap.org/cancerprotocols: College of American Pathologists 2021.
16. Köhler HF, Vartanian JG, Pinto CAL, Silva Rodrigues IFP, Kowalski LP (2022) The impact of worst pattern of invasion on the extension of surgical margins in oral squamous cell carcinoma. Head Neck 44(3):691–697. https://doi.org/10.1002/hed.26956
17. Seo G, Xing MH, Matloob A, Mundi N, Phan N, Samankan S, Khorsandi AS, Chai RL, Urken ML, Brandwein-Weber M. Extratumoral invasion: a unique phenomenon of agressive recurrent upper aerodigestive tract squamous cell carcinoma. Poster presentation presented at American Head and Neck Society 10th International Conference; 7/22/2021–7/25/2021, 2021.
18. Layfield EM, Schmidt RL, Esebua M, Layfield LJ (2018) Frozen section evaluation of margin status in primary squamous cell carcinomas of the head and neck: a correlation study of frozen section and final diagnoses. Head Neck Pathol 12(2):175–180. https://doi.org/10.1007/s12105-017-0846-6
19. Abbas SA, Ikram M, Tariq MU, Raheem A, Saeed J (2017) Accuracy of frozen sections in oral cancer resections, an experience of a tertiary care hospital. J Pak Med Assoc 67(5):806–809
20. Du E, Ow TJ, Lo Y-T, Gersten A, Schiff BA, Tassler AB, Smith RV (2016) Refining the utility and role of Frozen section in head and neck squamous cell carcinoma resection. Laryngoscope 126(8):1768–1775. https://doi.org/10.1002/lary.25899
21. Bogdanov-Berezovsky A, Rosenberg L, Cagniano E, Silberstein E (2008) The role of frozen section histological analysis in the treatment of head and neck skin basal and squamous cell carcinomas. Isr Med Assoc J 10(5):344–345
22. Sharma SM, Prasad BR, Pushparaj S, Poojary D (2010) Accuracy of intraoperative frozensection in assessing margins in oral cancer resection. J Maxillofac Oral Surg 8(4):357–361. https://doi.org/10.1007/s12663-009-0085-9
23. Ord RA, Aisner S (1997) Accuracy of frozen sections in assessing margins in oral cancer resection. J Oral Maxillofac Surg 55(7):663–669. https://doi.org/10.1016/S0278-2391(97)90570-X
24. Buchakjian MR, Tasche KK, Robinson RA, Pagedar NA, Sperry SM (2016) Association of main specimen and tumor bed margin status with local recurrence and survival in oral cancer surgery. JAMA Otolaryngol 142(12):1191–1198
25. Pathak KA, Nason RW, Penner C, Viallet NR, Sutherland D, Kerr PD (2009) Impact of use of frozen section assessment of operative margins on survival in oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107(2):235–239. https://doi.org/10.1016/j.tripleo.2008.09.028
26. Serinelli S, Bryant SM, Williams MPA, Marzouk M, Zaccarini DJ (2021) Frozen-permanent section discrepancy rate in oral cavity and oropharyngeal squamous cell carcinoma. Head Neck Pathol (Totowa, NJ) 16(2):466–475. https://doi.org/10.1007/s12105-021-01385-7
27. Moe J, McHugh JB, Udager AM, Braun TM, Helman JI, Ward BB (2019) Intraoperative depth of invasion is accurate in early-stage oral cavity squamous cell carcinoma. J Oral Maxillofac Surg 77(8):1704–1712. https://doi.org/10.1016/j.joms.2019.02.016
28. van Lanschot CGF, Klazen YP, de Ridder MAJ, Mast H, ten Hove I, Hardillo JA, Monserez DA, Sewnaik A, Meeuwis CA, Keereweer S, Aaboubout Y, Barroso EM, van der Toom QM, Bakker Schut TC, Wolvius EB, Baatenburg de Jong RJ, Puppels GJ, Koljenović S (2020) Depth of invasion in early stage oral cavity squamous cell carcinoma: the optimal cut-off value for elective neck dissection. Oral Oncol 111:104940–104940. https://doi.org/10.1016/j.oraloncology.2020.104940
29. Liu B, Amaratunga R, Veness M, Wong E, Abdul-Razak M, Coleman H, Gebski V, Sundaresan P (2020) Tumor depth of invasion versus tumor thickness in guiding regional nodal treatment in early oral tongue squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol 129(1):45–50. https://doi.org/10.1016/j.oooo.2019.08.002
30. Aaboubout Y, Toom Q, de Ridder M, de Herdt M, van der Steen B, van Lanschot F, Lamego Barroso E, Nunes Soares R, Hove I, Mast H, Smits R, Sewnaik A, Monserez D, Keereweer S, Caspers P, Baatenburg de Jong RJ, Bakker Schut T, Puppels G, Hardillo J, Koljenovic S (2021) Is the depth of invasion a marker for elective neck dissection in early oral squamous cell carcinoma? Front Oncol 11:628320–628320. https://doi.org/10.3389/fonc.2021.628320
31. Melchers LJ, Schuuring E, van Dijk BA, de Bock GH, Witjes MJ, van der Laan BF, van der Wal JE, Roodenburg JL (2012) Tumour infiltration depth ≥4 mm is an indication for an elective neck dissection in pT1cN0 oral squamous cell carcinoma. Oral Oncol 48(4):337–342. https://doi.org/10.1016/j.oraloncology.2011.11.007
32. Verma R, Singh A, Chowdhury N, Joshi PP, Durgapal P, Rao S, Kishore S (2021) Evaluation of histomorphological parameters to predict occult nodal metastasis in early-stage oral squamous cell carcinoma. Turk Patoloji Derg. https://doi.org/10.5146/tjpath.2021.01566(EvaluationofHistomorphologicalParameterstoPredictOccultNodalMetastasisinEarly-StageOralSquamousCellCarcinoma.)
33. Larson AR, Kemmer J, Formeister E, El-Sayed I, Ha P, George J, Ryan W, Chan E, Heaton C (2020) Beyond depth of invasion: adverse pathologic tumor features in early oral tongue squamous cell carcinoma. Laryngoscope 130(7):1715–1720. https://doi.org/10.1002/lary.28241
34. Shan J, Jiang R, Chen X, Zhong Y, Zhang W, Xie L, Cheng J, Jiang H (2020) Machine learning predicts lymph node metastasis in early-stage oral tongue squamous cell carcinoma. J Oral Maxillofac Surg 78(12):2208–2218. https://doi.org/10.1016/j.joms.2020.06.015

35. Samulski TD, La T, Wu RI (2016) Adaptive eLearning modules for cytopathology education: a review and approach: utility of adaptive eLEARNING. Diagn Cytopathol 44(11):944–951. https://doi.org/10.1002/dc.23558
36. Mills AM, Meyers-Needham M, LeGallo RD, Boyd JC, Cathro HP, Haverstick DM, La Fortune KA, Mills SE, Moskaluk CA, Stelow EB, Poulter MD, Stoler MH, Wick MR, Atkins KA (2014) From slide sets to sound bites: teaching and learning pathology in the digital age. J Am Soc Cytopathol JASC 3(4):183–187. https://doi.org/10.1016/j.jasc.2014.03.003
37. Chang Y-C, Nieh S, Chen S-F, Jao S-W, Lin Y-L, Fu E (2010) Invasive pattern grading score designed as an independent prognostic indicator in oral squamous cell carcinoma: Invasive pattern grading score in OSCC. Histopathology 57(2):295–303. https://doi.org/10.1111/j.1365-2559.2010.03616.x
38. Heerema MGJ, Melchers LJ, Roodenburg JLN, Schuuring E, de Bock GH, van der Vegt B (2016) Reproducibility and prognostic value of pattern of invasion scoring in low-stage oral squamous cell carcinoma. Histopathology 68(3):388–397. https://doi.org/10.1111/his.12754