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Predictors of locoregional control in stage I/II oral squamous cell carcinoma classified by AJCC 8th edition

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ABSTRACT

Objectives: To study the determinants of locoregional control (LRC) on stage I/II oral squamous cell carcinoma (OSCC) classified by AJCC 8th edition.
Methods: Retrospective analysis from 296 patients of pT1-2N0 oral OSCC treated with surgery (wide local excision and selective neck dissection). Those receiving adjuvant therapy were excluded. Multivariate analysis was performed for impact of adverse pathological features (APFs) on LRC.
Results: In stage I, LRC was impacted by perineural invasion (PNI) (HR 7.72, $p = 0.010$, 95% CI 1.64–36.26) and moderate/poor differentiation (MD/PD) (HR 3.04, $p = 0.049$, 95% CI 0.99–9.25). In stage II, LRC was impacted by depth of invasion (DOI) (HR 1.59, $p = 0.014$, 95% CI 1.099–2.32), PNI (HR = 2.86, $p = 0.005$, 95% CI 1.36–5.98). Combined MD/PD and PNI were associated with worse LRC than either feature individually (HR = 4.12, $p < 0.001$, 95% CI 2.16–7.85).
Conclusion: PNI and differentiation accurately predict LRC in AJCC 8th edition classified stage I/II OSCC. PNI was a stronger predictor of locoregional failure than DOI in stage II disease. By incorporating these parameters, we can improve precision in staging of early OSCC and identify potential candidates for treatment escalation to improve outcomes.

Background

The incorporation of depth of invasion (DOI) into TNM staging by the American Joint Committee on Cancer 8th edition [1] has resulted in a paradigm shift in pathological staging of oral squamous cell carcinoma (OSCC). Tumours having a DOI <5 mm have been designated as T1, those with a DOI of 5–10 mm T2 and those with DOI >10 mm as T3. Given that DOI is a superior predictor of disease specific survival than tumour diameter alone [2], it is possible that it is a surrogate marker for tumour biology, with limited diameter but extensive infiltration being more clinically aggressive than thick exophytic tumours.

Stage I/II OSCC has been shown to have favourable outcomes, however an estimated 30–35% of patients have loco-regional recurrences [3]. Identifying predictors of recurrence in this cohort is therefore of prime importance, to consolidate treatment and offer these patients the highest chance of cure. The role of histological adverse pathological features (APFs) is well established; several factors have been demonstrated to predict tumour behaviour and the risk of recurrence. DOI, invasive fronts, close/involved margins, perineural invasion (PNI), lymphovascular invasion (LVI), and poor differentiation were initially used to predict the need for elective neck dissection in view of the risk of occult lymph node metastasis [4–6], and more recently as indicators for post-operative radiotherapy (PORT) [7–9].

With the adoption of the new staging system, the role of APFs in tumours classified as stage I/II OSCC by AJCC 8th edition is unclear; all of the previous evidence has taken tumour diameter as the only determinant for staging and incorporation of DOI is likely to cause significant stage migration in these patients, resulting in even more

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uncertainty in an already contentious cohort. The purpose of this study was to identify factors associated with poor loco-regional control in patients reclassified as stage I/II by AJCC 8th edition who were treated with surgery alone. In doing so, we hoped to identify patients with the 'new' intermediate-stage early oral cancer, who would potentially benefit from treatment escalation.

Materials and methods

From a prospectively maintained database of patients treated in our institution, Amrita Institute of Medical Sciences, Kochi, between 2006 and 2014, we identified 296 patients of OSCC (tongue, floor of mouth and buccal mucosa) classified as pT1-2N0 by AJCC 8th edition (those with diameter <2 cm and DOI ≤5 mm staged as pT1 and those with diameter 2–4 cm or DOI 6–10 mm staged as pT2). To avoid bias, we included consecutive patients; all patients treated during this period who fulfilled the inclusion criteria were included. All patients were treated with wide excision of the lesion (a gross margin of 1–1.5 cm aiming for a minimum microscopic margin of 5 mm) and ipsilateral selective neck dissection, and appropriate reconstruction when required. Those with a closest radial margin below 5 mm during primary excision (even if subsequently revised) and those who received any prior therapy or adjuvant therapy were excluded. In view of the retrospective nature of the study it was exempt from ethical clearance.

Information extracted from this database included age, gender, tumour pathological stage, adverse pathological features, development of recurrences, pattern of recurrence, treatment details, status at last follow-up, disease free survival and overall survival. Reporting of differentiation was done based on Broder's grading system [10] and perineural or lymphovascular invasion was reported as positive when at least 33% of the nerve or vessel was surrounded by tumour cells [11]. In our cohort any identifiable area of nerve or lymphatic vessel invasion satisfying this criterion, irrespective of size and focality, was considered positive. For assessment of DOI, patients treated between 2010 and 2014 (n = 264) had DOI specifically measured and mentioned on histology reports, while for those treated from 2006 to 2009 (n = 32), patients had either DOI or tumour thickness mentioned often interchangeably. Slide and block review for the cohort treated between 2006 and 2009 was not possible due to logistical difficulties. Given that it has been shown that when DOI is not available, tumour thickness can be used as a reasonable substitute in the AJCC 8th edition staging system [12], we included these cases in our analysis as well.

Recurrent disease was defined as any proven local, regional or distant disease occurring at least three months after date of surgery. Locoregional control was defined as time from surgery to occurrence of local or nodal disease.

Statistical analysis was performed using STATA version 14 (StataCorp, TX, USA), Excel version 2010 (Microsoft, Redmond, WA, USA). The endpoint for analysis was disease free survival (DFS). Survival curves were generated using the Kaplan Meier method and log rank test. Univariate analysis for categorical data was performed with chi-square test. Multivariate analysis was performed using the Cox proportional hazards model. All statistics were 2-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient and disease and characteristics

Patient, treatment and disease characteristics for our cohort of stage I/II OSCC is shown in Table 1. The median age of our patients was 55.2 years (range 18–78 years), with males accounting for 78% of our cohort. DOI correlated well with tumour diameter; for pT1 tumours (DOI<5 mm), mean diameter was 14.4 mm, while for pT2 tumours (DOI 6–10 mm), mean diameter was 26.7 mm. However, the median least tumour margin was comparable between the two groups - 7.86 mm and 7.84 mm for pT1 and pT2 respectively. The nodal yield on neck dissection between the two groups was also comparable and adequate; only 2 patients in the entire cohort (0.7%) had a nodal yield <18 nodes (see Table 2).

The incidence of APFs was seen to correlate significantly with T-stage. PNI was seen in 12% of stage I and 40% of stage II ($p < 0.001$), LVI was associated with 13% of stage I and 47% of stage II ($p < 0.001$) and moderate/poor differentiation was noted in 35% of stage I and 53% of stage II patients ($p < 0.001$) on univariate analysis.

Impact of adverse pathological features on locoregional control

The median follow-up in our cohort was 28 months (range, 6–132 months) with a 5-year overall survival (OS) of 90% and 88% for stage I and II respectively, and a locoregional control (LRC) of 70% and 60% for stage I and II respectively.

For stage I OSCC, PNI had a significant impact on LRC by multivariate analysis (HR 7.72, $p = 0.010$, 95% CI 1.64–36.26); the presence of any PNI on histology was associated with almost eight times higher risk of a locoregional recurrence. Moderate or poor differentiation (MD/PD) was also found to have a significant impact on LRC by multivariate analysis (HR 3.04, $p = 0.049$, 95% CI 0.99–9.25), with moderately or poorly differentiated tumours having three-times higher likelihood of a locoregional recurrence when compared to patients with well-differentiated tumours. LVI, however, was not a

Table 1
Patient, treatment and disease characteristics (according to AJCC 8th edition).

		pT1N0	pT2N0	p-value
Total: 296 patients		154	142	
Sex	F	34	32	0.346
	M	120	110	
Age		55.2 ± 13.3	55.1 ± 13.3	0.673
Least margin (mm)		7.86 ± 3.12	7.84 ± 3.14	0.176
Diameter (mm)		14.4 ± 3.9	26.7 ± 5.3	<0.001
Perineural invasion (%)		19 (12%)	57 (40%)	<0.001
Lymphovascular invasion (%)		20 (13%)	41 (47%)	<0.001
Differentiation (%)	Well	100 (65%)	67 (47%)	0.001
	Moderate	50 (33%)	70 (50%)	
	Poor	4 (2%)	5 (3%)	
Nodal yield on neck dissection (n, range)		22 (16-68)	20 (18-74)	0.753
Recurrences		42 (27%)	36 (25%)	0.707
Locoregional recurrence		31 (74%)	30 (83%)	0.627
Distal recurrence		11 (23%)	6 (17%)	

Table 2
Predictors of locoregional control stage-wise on multivariate analysis by Cox proportional hazards regression model.

	Hazard ratio	p-value	95% confidence interval	
Stage I	Referent			
LVI	1.21	0.699	0.159	3.423
PNI	7.72	0.010*	1.64	36.26
MD/PD	3.04	0.049*	0.99	9.25
PNI and MD/PD	8.67	0.006*	1.84	40.76
Stage II	Referent			
DOI	1.59	0.014*	1.099	2.32
LVI	1.08	0.744	0.361	2.133
PNI	2.86	0.005*	1.36	5.98
MD/PD	1.62	0.141	0.85	3.08
PNI and MD/PD	4.12	<0.0001	2.16	7.85

Key: LVI – lymphovascular invasion, PNI – perineural invasion, MD – moderate differentiation, PD – poor differentiation.

significant predictor of LRC. When looking at a combination of adverse features, it was noted that stage I tumours with both PNI and MD/PD, had a very poor locoregional control rate (HR = 8.67, p = 0.006, 95% CI 1.84–40.76); these patients had a nearly nine-times higher risk of locoregional relapse by multivariate analysis.

LCR rates are reflected in Fig. 1 as plotted by the Kaplan Meier method; LCR for stage I without APFs, with MD/PD, with PNI and with both MD/PD and PNI was 92%, 75%, 50% and 27% respectively. PNI and MD/PD individually impacted LCR in stage I OSCC but in combination their effect was profound. It is to be noted, however, that only 6 patients had both PNI and MD/PD (4% of the cohort); hence multiple APFs in stage I OSCC occurred rarely.

For stage II OSCC, we first considered the impact of DOI on locoregional control. Using stage I (diameter <2 cm and DOI ≤5 mm) as the referent cohort, we looked at the effect of DOI 5–10 mm had on locoregional control. Increasing DOI was associated with poorer LRC; tumours with DOI 5–10 mm had a 60% higher chance of locoregional failure by multivariate analysis (HR 1.59, p = 0.014, 95% CI 1.099–2.32). PNI again had a significant impact on LRC by multivariate analysis (HR = 2.86, p = 0.005, 95% CI 1.36–5.98), with locoregional failure being almost thrice as likely in patients with any PNI noted on histology. MD/PD was associated with a slightly lower LRC than well-differentiated tumours, but this effect was not statistically significant by multivariate analysis (HR = 1.62, p = 0.141, 95% CI 0.85–3.08). LVI was not a significant predictor of locoregional recurrence in this cohort. As with stage I OSCC, a combination of PNI and MD/PD was predictive of a significantly higher risk of locoregional failure than either factor individually by multivariate analysis (HR = 4.12, p < 0.001, 95% CI 2.16–7.85). Unlike in stage I OSCC, the association of PNI and MD/PD was not rare; 28 patients (20%) with stage II OSCC had both of these adverse features on histology.

5-year LCR for stage II OSCC is shown in Fig. 2; the LRC for stage II without APFs, with MD/PD, with PNI and with both MD/PD and PNI was 78%, 72%, 48% and 25% respectively.

Discussion

Reclassification of OSCC by AJCC 8th edition by incorporating DOI resulted in better prognostic grouping. This was reflected in a good stratification of APFs; stage II had a significantly higher association of LVI, PNI and poorer differentiation when compared with those having stage I disease.

As expected, DOI was an independent predictor of locoregional control on multivariate analysis, with node-negative tumours with DOI 5–10 mm having a 60% higher chance of locoregional failure than those with DOI <5 mm. Like other recent publications, our findings validate the impact of DOI in early oral cancer [13,14] and reiterate that DOI is an independent adverse pathological feature independent of propensity for nodal spread [15,16]. Interestingly, the HR for DOI >5 mm in our cohort was 1.59 for LRC, which was comparable to the HR for OS (1.56) in a recent large National Cancer Data Base review of nearly forty thousand patients [16]; this may be a reaffirmation of our belief that LRC is a good surrogate marker for OS in T1/2 tumours.

LVI failed to predict recurrence in our cohort. Previous studies [18–20] have shown the impact of LVI on recurrence and survival

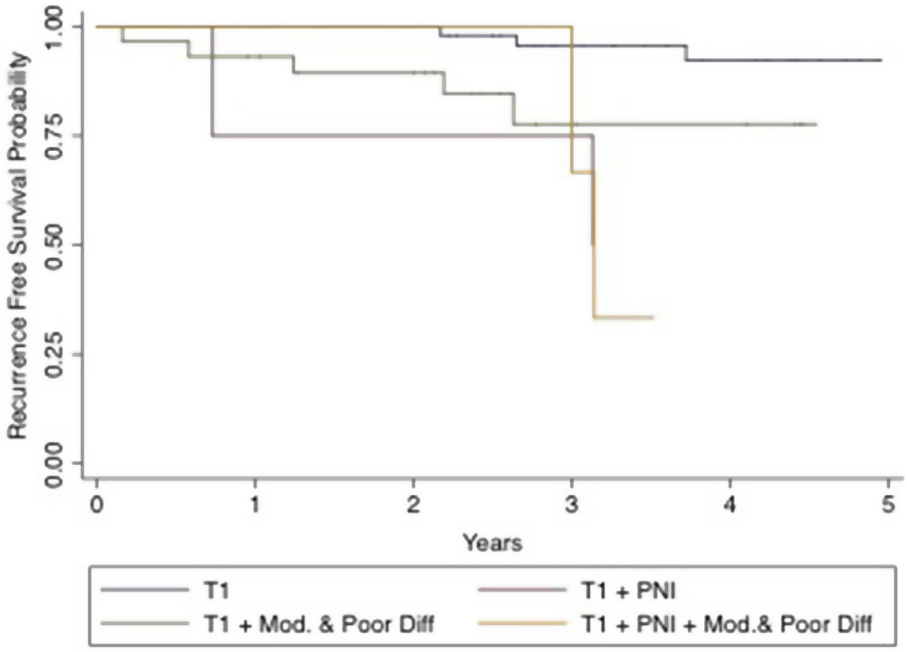

Fig. 1. Locoregional control in pT1N0 OSCC with adverse pathological features.

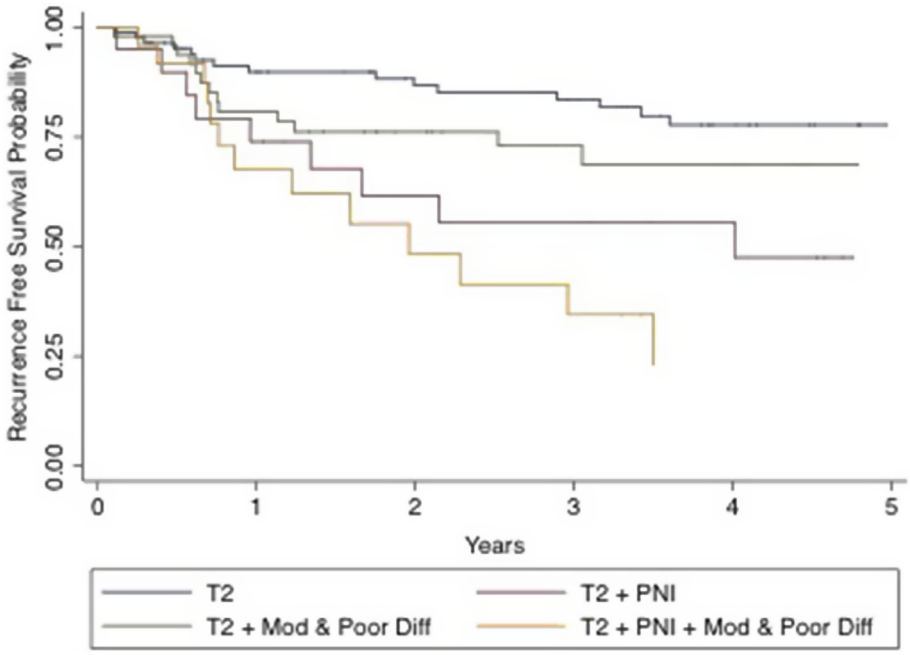

Fig. 2. Locoregional control in pT2N0 OSCC with adverse pathological features.

however this premise has been based on the association with occult nodal metastases; all of the patients in our cohort received elective neck dissection. It is interesting to note that studies showing LVI as a prognostic factor [21,22] were those without elective treatment of the neck; whether elective neck dissection significantly mitigates the risk associated with LVI in unclear and requires further study. More recent data has shown that LVI is a strong prognostic determinant in advanced OSCC (T3/4) but not early cancer (T1/2) [23]. The potential reason for this observation is controversial and not well substantiated; it is believed that early stage OSCC patients with LVI are at risk for nodal failure, which may be pre-empted by an elective neck dissection, while advanced stage OSCC patients with LVI are at risk for distal failure, the risk of which may not be completely addressed with PORT.

The incidence of PNI in our cohort was high compared to existing literature. PNI was seen in 12% of stage I and 40% of stage II OSCC in our cohort; in comparison, it has been seen in only 10–20% of patients with early OSCC [24,25]. The reason for this disparity is likely our definition of PNI on histology; we included any patient with nerve involvement in >33% of the nerve circumference as 'positive' in our analysis, however other studies may have been more selective. The only standard definition for PNI in literature is involvement of over 33% of the nerve circumference, though multiple other stratifications exist, including unifocal or multifocality, small nerve ($\leq$1 mm diameter), large nerve (>1 mm diameter) and 'named' nerve involvement. Although it has been demonstrated that these distinctions may impact prognosis [26], it was our intention to use a broad definition of PNI in this study in order to make our results as widely applicable and relevant as possible; many centres do not have dedicated onco-pathologists, and many patients of OSCC in the developing world are not treated in cancer centres, hence we intended to determine if we could use simple well-established histological criteria to improve precision in staging. *Any* PNI, when identified in histology, was a strong, independent predictor of locoregional recurrence in stage I/II OSCC; hence our data suggests that inclusion of any PNI noted on histology is a reasonable approach to improve the precision of AJCC 8th edition staging in early stage oral cancer.

Differentiation was also a strong prognostic determinant in stage I/II OSCC. First described by Broder in 1920 [10,27], grading of squamous cell carcinoma has been shown to be associated with both recurrence and survival [28–30]. Further refinements were made by incorporation of host-tumour interface [31] and other morphological features like degree of keratinization, nuclear polymorphism and number of mitoses [32]. Although attractive, the complexities of these grading systems and inter-observer variation preclude their routine use in clinical practice, even in specialized centres. Further confusion arises when a recommendation of PORT needs to be made on these staging systems, where two pathologists may not concur.

When considering differentiation as an APF, we grouped moderate and poor differentiation and compared them to well differentiated tumours as a reference. This was because very few tumours in our cohort were classified as poorly differentiated (3%); a significantly larger proportion of tumours, however, were classified as moderate-to-poorly differentiated (17%). This grouping allowed us to make a more reasonable comparison. Additionally, we believe that this may, to some extent, address the inter-observer variability in OSCC differentiation reporting, which has been well established [33]. It also reduces potential confusion when different parts of the tumour have different grades.

Our incidence of MD/PD is comparable to literature [23,24]; well-differentiated tumours accounted for 65% of stage I patients but only 47% of stage II. MD/PD had a hazard ratio of 3.04 for locoregional recurrence in stage I ($p = 0.049$), while in stage II the hazard ratio was 1.62 ($p = 141$). Given the large proportion of moderately differentiated tumours in stage II (50%), it is likely that considering moderate-to-poor differentiation or poor differentiation (excluding moderate differentiation) as an adverse feature would be a better predictor of recurrence in larger tumours. It is likely that as tumour size increases, the impact of MD/PD on LRC reduces. However it is important to note that the combination of MD/PD and PNI in stage II OSCC has a significantly worse LCR than ($HR = 4.12$) than PNI ($HR = 2.86$) or MD/PD ($HR = 1.62$) individually, which suggests differentiation cannot be completely excluded as an APF; a moderately-differentiation pT2N0 tumour with PNI has a

risk of locoregional failure four times higher than a well-differentiated pT2N0 tumour. It is our belief that refinement of the pathological reporting would demonstrate this distinction, however it was not possible to perform it in this cohort of patients due to logistical constraints.

Although AJCC 8th edition has significantly improved OSCC staging by incorporating DOI into T-stage, is it adequate for early stage tumours? Our recent publication [34] showed that AJCC 8th edition staging better predicted overall survival for T1/2 tumours, however we considered node positive patients as well. We demonstrated that the hazard ratio for death in patients with T1/2 OSCC was 2.46 in PNI and 2.19 in MD/PD, in spite of 63% of these patients receiving adjuvant radiotherapy or chemoradiotherapy. Hence for patients with stage I/II disease who do not receive PORT, the impact of these adverse features are likely to be even more marked.

In our cohort of stage II tumours as described in this study, DOI 5–10 mm increases the risk of locoregional failure by 60%, whereas PNI increased this risk of by 186%. MD/PD also increased this risk by 62%, although it was not statistically significant. It is our opinion that incorporation of DOI alone into tumour staging is unsatisfactory for early stage tumours; without accounting for other adverse features the staging system is insufficient and inadequate. By incorporating PNI and differentiation into the new classification, we were able to better prognosticate early stage OSCC. Based on the presence of PNI and MD/PD, LRC ranged between 92% and 27% for stage I and 78% and 25% for stage II OSCC; it is our belief that incorporation of these well-established APFs into staging significantly improved its precision in staging early OSCC.

Although there is no consensus on the role of PORT in PNI and poor differentiation in early OSCC, our data would suggest that these patients may benefit from treatment escalation since the pattern of failure in these patients was predominantly locoregional (88%); in the presence of adequate margins and an adequately dissected neck, PORT is a reasonable addition to surgery to improve LRC in intermediate-risk early stage OSCC. Although no high quality evidence exists to determine the use of PORT in early OSCC, it is crucial to attempt to identify intermediate-risk patients who would benefit from PORT to prevent recurrence and potentially improve survival.

Conclusion

DOI alone is insufficient to predict LRC in early stage OSCC. Until other adverse features are integrated into the staging system, the prediction of LRC in early OSCC will be imprecise. Our results suggest that by incorporating PNI and differentiation into staging for early stage OSCC, patients at higher risk of locoregional failure are effectively identified for potential treatment escalation.

References

[1] Amin Mahul B, Edge Stephen B, Greene Frederick L. AJCC cancer staging manual. eighth ed. Springer; 2017 [Print].

[2] Ebrahimi A, Gil Z, Amit M, Yen TC, Liao CT, Chaturvedi P, et al. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA Otolaryngology–Head & Neck Surgery 2014 Dec 1;140(12):1138–48.

[3] Liao CT, Chang JT, Wang HM, et al. Salvage therapy in relapsed squamous cell carcinoma of the oral cavity: how and when? Cancer 2008 Jan 1;112(1):94–103.

[4] Sparano A, Weinstein G, Chalian A, Yodul M, Weber R. Multivariate predictors of occult neck metastasis in early oral tongue cancer. Otolaryngol Head Neck Surg 2004;131:472–6.

[5] Ebrahimi A, Ashford BG, Clark JR. Improved survival with elective neck dissection in thick early- stage oral squamous cell carcinoma. Head Neck 2012;34. 709–16.

[6] Huang S, Hwang D, Lockwood G, Goldstein D, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity. Cancer 2009;115:1489–97.

[7] Fang FM, Leung SW, Huang CC, et al. Combined modality therapy for squamous cell carcinoma of the buccal mucosa: treatment and prognostic factors. Head Neck 1997;19(6). 506–12.

[8] El-Husseiny G, Kandil A, Jamshed A, et al. Squamous cell carcinoma of the oral tongue: an analysis of prognostic factors. Br J Oral Maxillofac Surg 2000;38(3).

[9] Low H, Gao K, Gupta R, et al. Factors predicting poor outcomes in T1N0 oral squamous cell carcinoma: indicators for treatment intensification. ANZ J Surg 2016;86:366–71.

[10] Tumours and cysts of the dermis. In: Lever WF, Schaumherg-Lever G, editors. Histopathology of the skin. Philadelphia: J. B. Lippincott; 1983. p. 472–521.

[11] Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion in squamous cell carcinoma of the head andneck. Arch Otolaryngol Head Neck Surg 1998;124(6):637–40.

[12] Dirven R, Ebrahimi A, Moeckelmann N, Palme CE, Gupta R, Clark J. Tumor thickness versus depth of invasion–Analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. Oral Oncol 2017 Nov 1;74:30–3.

[13] Vuity D, McMahon J, Takhiuddin S, Slinger C, McLellan D, Wales C, et al. Is the 8th edition of the Union for International Cancer Control staging of oral cancer good enough? Br J Oral Maxillofac Surg 2018 Mar 22;(18):30038–X. pii: S0266-4356.

[14] Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual.CA. A Cancer Journal for Clinicians 2017;67(2):122–37. 1.

[15] Liao CT, Lin CY, et al. Identification of a high-risk group among patients with oral cavity squamous cell carcinoma and pT1–2N0 disease. Int J Radiat Oncol Biol Phys 2012;82:284–90.

[16] Almangush A, Bello IO, Keski–Säntti H, Mäkinen LK, Kauppila JH, Pukkila M, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. Head Neck 2014;36(6):811–8.

[18] Maddox WA, Urist MM. Histopathological prognostic factors of certain primary oral cavity cancers. Oncology (Hunting) 1990;4(12):39–42.

[19] Resnick JM, Uhlman D, Niehans GA, et al. Cervical lymph node status and survival in laryngeal carcinoma: prognostic factors. Ann Otol Rhinol Laryngol 1995;104(9):685–94.

[20] Magnano M. Bongioa.nnini G, Lerda W. Lymphnode metastasis in head and neck squamous cells carcinoma: multivariate analysis of prognostic variables. J Exp Clin. Cancer Res 1999;18(1):79–83.

[21] Close LG, Brown PM, Voitch MF, et al. Microvascular invasion and survival in cancer of the oral cavity and oropharynx. Ann Otolaryngol Head Neck Surg 1989;115(11):1304–9.

[22] Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in patients with lymph node involvement 1994;120(12):1370–4. Arch Otolaryngol Head Neck Surg.

[23] Liu SA, Wang CC, Jiang RS, Lee FY, Lin WJ, Lin JC. Pathological features and their prognostic impacts on oral cavity cancer patients among different subsites–A single institute's experience in Taiwan. Sci Rep 2017 Aug 7;7(1):7451.

[24] Fried D, Mullins B, Weissler M, Shores C, Zanation A, Hackman T, et al. Prognostic significance of bone invasion for oral cavity squamous cell carcinoma considered T1/T2 by American joint committee on cancer size criteria. Head Neck 2014 Jun;36(6):776–81.

[25] Nair D, Mair M, Singhvi H, Mishra A, Nair S, Agrawal J, Chaturvedi P. Perineural invasion: independent prognostic factor in oral cancer that warrants adjuvant treatment. Head Neck 2018;40(8):1780–7.

[26] Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. 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 2005;29(2):167–78.

[27] Broders AC. Squamous-cell epithelioma of the lip. J Am Med Assoc 1920;74(10):656–64.

[28] Olsen KD, Caruso M, Foote RL, et al. Primary head and neck cancer. Histopathologic predictors of recurrence after neck dissection in pa- tients with lymph node involvement 1994;120(12):1370–4. An:h Otolaryngol Head Neck Surg.

[29] Beenken SW, Krontiras H, Maddox WA, et al. Tl and T2 squamous cell carcinoma of the oral tongue: prognostic factors and the role of elective lymph node dissection. Head Neck 1999;21(2):124–30.

[30] Roland NJ, Caslin AW, Nash J, et al. Value of grading squamous cell carci- noma of the head and neck. Head Neck 1992;14(3):224–9.

[31] Jakobsson PA, Eneroth CM, Killander D, et al. Histologic classification and grading of malignancy in carcinoma of the larynx. Acta Radiol Ther Phys Biol 1973;12(1):1–8.

[32] Anneroth G, Batsakis J, Luna M. Review of the literature and a recom- mended system of malignancy grading in oral squamous cell carcinomas. Scal!d J Dent Res. 1987;95(3):229–49.

[33] Karabulut A, Reibel J, Therkildsen MH, Praetorius F, Nielsen HW, Dabelsteen E. Observer variability in the histologic assessment of oral premalignant lesions. J Oral Pathol Med 1995 May 1;24(5):198–200.

[34] Subramaniam N, Murthy S, Balasubramanian D, et al. Adverse pathologic features in T1/2 oral squamous cell carcinoma classified by the American Joint Committee on Cancer eighth edition and implications for treatment. Head Neck 2018;1–7.