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Small oral tongue cancers (≤ 4 cm in diameter) with clinically negative neck: from the 7th to the 8th edition of the American Joint Committee on Cancer

Alhadi Almangush [1,2,3] · Antti A. Mäkitie [4,5] · Laura K. Mäkinen [4] · Joonas H. Kauppila [6,7] · Matti Pukkila [8] ·
Jaana Hagström [1,9,10] · Jussi Laranne [11] · Ylermi Soini [12] · Luiz Paulo Kowalski [13] · Reidar Grénman [14] · Caj Haglund [10,15] ·
Ricardo D. Coletta [16] · Tuula Salo [1,6,17] · Ilmo Leivo [2]

Abstract

One of the main changes in the 8th edition of the American Joint Committee on Cancer (AJCC) for staging of oral cancer is the inclusion of depth of invasion (DOI) in the T category. However, cancers in different oral subsites have variable behavior, with oral tongue squamous cell carcinoma (OTSCC) being the most aggressive one even at early stage. Thus, it is necessary to evaluate the performance of this new T category in homogenous cohort of early OTSCC. Therefore, we analyzed a large cohort of patients with a small (≤ 4 cm) OTSCC to demonstrate the differences in T stage between the AJCC 7th and 8th editions. A total of 311 early-stage cases (AJCC 7th) of OTSCC were analyzed. We used 5 mm and 10 mm DOI for upstaging from T1 to T2 and from T2 to T3 respectively, as in the AJCC 8th. We further reclassified the cases according to our own proposal suggesting 2 mm to upstage to T2 and 4 mm to upstage to T3. According to AJCC 7th, there were no significant differences in the survival analysis. When we applied the 8th edition, many cases were upstaged to T3 and thus associated with worse disease-specific survival (HR 2.37, 95% CI 1.12–4.99) and disease-free survival (HR 2.12, 95% CI 1.09–4.08). Based on our proposal, T3 cases were associated with even worse disease-specific survival (HR 4.19, 95% CI 2.27–7.74). The 8th edition provides better survival prediction for OTSCC than the 7th and can be further optimized by lowering the DOI cutoffs.

Keywords Early-stage · Oral tongue cancer · Depth of invasion · 7th AJCC · 8th AJCC

✉ Alhadi Almangush
   alhadi.almangush@helsinki.fi; alhadi.almangush@gmail.com

1   Department of Pathology, University of Helsinki, Haartmaninkatu 3 (P.O. Box 21), FIN-00014 Helsinki, Finland

2   Department of Pathology, University of Turku, Turku, Finland

3   Institute of Dentistry, University of Misurata, Misurata, Libya

4   Department of Otorhinolaryngology - Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

5   Division of Ear, Nose and Throat Diseases, Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

6   Cancer and Translational Medicine Research Unit, Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland

7   Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

8   Department of Otorhinolaryngology and Head and Neck Surgery, Kuopio University Hospital, Kuopio, Finland

9   HUSLAB, Department of Pathology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

10 Research Programs Unit, Translational Cancer Biology, University of Helsinki, Helsinki, Finland

11 Department of Otorhinolaryngology and Head and Neck Surgery, Tampere University Hospital, Tampere, Finland

12 Department of Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland

13 Department of Head and Neck Surgery and Otorhinolaryngology, A.C. Camargo Cancer Center, São Paulo, -SP, Brazil

14 Department of Otorhinolaryngology - Head and Neck Surgery, Turku University Hospital, University of Turku, Turku, Finland

15 Department of Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

16 Department of Oral Diagnosis, School of Dentistry, State University of Campinas, Piracicaba, São Paulo, Brazil

17 Department of Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland

Introduction

Tumor-Node-Metastases (TNM) staging system is widely used as a universal tool for the classification of many cancers. TNM staging defines extent of tumor and provides prognostic information, which is traditionally used for treatment planning [1]. Treatment of small tumors (T1–T2) of oral tongue squamous cell carcinoma (OTSCC) with clinically negative neck (cN0) still remains a dilemma. Although such cancers are considered at "early-stage" and referred to "low-risk," many of the cT1–2N0 cases have been associated with poor prognosis [2, 3]. Therefore, cTNM has been criticized over the years for presenting low prognostic capacity for early-stage OTSCC [4]. The main shortcoming of the T stage category is that it describes only the tumor diameter. Thus, a small superficial tumor with < 4 cm in diameter is considered (according to the 7th edition of the American Joint Committee on Cancer, AJCC manual [5]) at early-stage, similar to another small tumor < 4 cm in diameter but with deeper invasion.

The AJCC has recently released the 8th edition of manual for cancer staging [6]. For oral squamous cell carcinoma (OSCC), one of the main changes in this new edition was the incorporation of depth of invasion (DOI) in the T category. Researchers have conducted numerous studies to evaluate the prognostic value of DOI in OSCC [3, 4, 7]. There is a wide agreement between most of the recent studies about the importance of DOI in prognostication of OSCC [3, 7, 8]. However, a debate about the optimal cutoff point remains among the published studies. For example, cutoff points of 2 mm [9], 4 mm [3, 10], and 5 mm [11] have been used for risk stratification. AJCC has used > 5 mm for upstaging from T1 to T2 and > 10 mm for upstaging to T3. The aim of this study was to demonstrate the effects of changes regarding T stage between the AJCC 7th and 8th editions [5, 6] in a multicenter cohort of 311 cases previously identified as early stage according to AJCC 7th edition [5]. We also provide a proposal for the future developmental work of the AJCC system to further optimize the criteria for T category. Our proposal is based on evidence from a meta-analysis that found 4 mm as an optimal cutoff point [12] for risk stratification. Of note, many subsequent studies had validated the finding of that meta-analysis and confirmed that early OTSCC tumors deeper than 4 mm associated with high risk of poor prognosis [3, 7, 13].

Materials and methods

This retrospective study included patients treated for OTSCC at the five Finnish university hospitals (224 cases) and in the A.C. Camargo Cancer Center, São Paulo, Brazil (87 cases). According to the AJCC 7th staging (Table 1) [5], these cases were identified as early stage (T1–T2N0); and were all surgically treated. We used the criteria for T stage introduced in the AJCC 8th (Table 1) [6] to re-stage these 311 cases by including depth of invasion (DOI), which was measured as described by the AJCC [6]. In the AJCC 8th, T1 refers to tumors ≤ 2 cm in diameter and DOI ≤ 5 mm. T2 refers to tumors ≤ 2 cm in diameter and DOI > 5 mm and ≤ 10 mm, or tumors > 2 cm but ≤ 4 cm and DOI ≤ 10 mm. T3 refers to tumors > 4 cm or any tumors with DOI > 10 mm. T4 refers to moderately advanced or very advanced local disease. According to the AJCC 8th, DOI does not influence the T4 stage. We also re-staged these 311 cases using our proposal (Table 1) as follows: T1, tumor ≤ 2 cm and DOI ≤ 2 mm; T2, tumor ≤ 2 cm and DOI > 2 mm and ≤ 4 mm, or tumor > 2 cm but ≤ 4 cm and DOI ≤ 4 mm; T3: tumor > 4 cm or any tumor DOI > 4 mm.

Statistical analysis was performed using SPSS 24.0. Univariate and multivariate logistic regression was used to assess the relationship between T stage (AJCC 7th, AJCC 8th and our proposal) and the disease-specific survival (DSS) or disease-free survival (DFS). DSS was defined as the time from surgery to death due to OTSCC or to the time point of the last follow up. DFS was defined as the time from surgery to recurrence at the site of the primary tumor, in neck lymph nodes, or both, or to the time point of the last follow-up. Survival analysis was also conducted by Kaplan-Meier analysis and log-rank test. Hazard ratios (HR) and 95% confidence interval (95% CI) were calculated by Cox regression. P value < 0.05 was considered statistically significant.

Results

This study includes 165 men and 146 women. One hundred five tumors were well differentiated, 131 were moderately differentiated, and 75 tumors were poorly differentiated. According to the AJCC 7th, 124 cases were of stage T1 and 187 cases were of stage T2. Survival analyses (Table 2) did not show any statistically significant differences for DSS (HR 1.48, 95% CI 0.87–2.54, $P = 0.15$) or DFS (HR 0.87, 95% CI 0.57–1.33, $P = 0.53$) when we analyzed the prognostic value of T stage in these 311 cases.

When we re-staged the cases according to the criteria of the AJCC 8th, 90 cases were of stage T1, 201 were of T2, and 20 cases were of T3. Univariate survival analyses showed statistically significant differences in the prognosis of the cases identified as T3 (Table 2 and Fig. 1). They were associated with worse DSS (HR 2.21, 95% CI 1.05–4.64, $P = 0.036$) and DFS (HR 2.08, 95% CI 1.07–4.01, $P = 0.03$) compared with early-stage cases (T1–T2). There was no statistically significant difference between T1 and T2 cases. In multivariate analysis, which includes age of patient, gender, and WHO histologic grade, small tumors (≤ 4 cm in diameter, with cN0)

Table 1 T staging criteria for small OTSCC (≤ 4 cm in diameter) with clinically negative neck in the AJCC 7th, the AJCC 8th (which incorporated depth of invasion, DOI (DOI is the measurement of depth of invasion and not tumor thickness)), and our proposal using a lower cutoff point for DOI

T category	Criteria in the AJCC 7th	Criteria in the AJCC 8th	Our proposal
T1	Tumor ≤ 2 cm	Tumor ≤ 2 cm, ≤ 5 mm DOI	Tumor ≤ 2 cm, ≤ 2 mm DOI
T2	Tumor > 2 cm but ≤ 4 cm	Tumor ≤ 2 cm, DOI > 5 mm and ≤ 10 mm; or tumor > 2 cm but ≤ 4 cm, and ≤ 10 mm DOI	Tumor ≤ 2 cm, DOI > 2 mm and ≤ 4 mm; or tumor > 2 cm but ≤ 4 cm, and ≤ 4 mm DOI
T3	–	Tumor > 4 cm or any tumor > 10 mm DOI	Tumor > 4 cm or any tumor > 4 mm DOI

identified as T3 (AJCC 8th) were associated with worse DSS (HR 2.37, 95% CI 1.12–4.99, $P = 0.023$) and DFS (HR 2.12, 95% CI 1.09–4.08, $P = 0.027$).

According to our proposal, 32 cases were of stage T1, 118 were of T2, and 161 cases were of stage T3. Survival analyses (Table 2 and Fig. 2) showed statistically significant differences and the cases identified as stage T3 were associated with worse DSS (HR 3.87, 95% CI 2.10–7.13, $P < 0.001$) and DFS (HR 1.55, 95% CI 1.01–2.37, $P = 0.04$). There was no statistically significant difference between stage T1 and T2 cases. In the multivariate analysis, cases that were identified as T3 were associated with worse DSS (HR 4.19, 95% CI 2.27–7.74, $P < 0.001$) and DFS (HR 1.62, 95% CI 1.05–2.49, $P = 0.029$).

The association analysis of age, gender, and WHO histopathologic grade with T stage (AJCC 7th) revealed a significant relationship between gender and T stage, as men were more affected by T2 tumors than women ($P = 0.008$). Similarly, applying the AJCC 8th, men were more affected by T2 and T3 tumors than women ($P = 0.02$). There was no significant relationship between T stage (AJCC 7th or AJCC 8th) and age of patients or WHO tumor grade. Our proposed T stage had a significant association with WHO grade ($P = 0.02$), but there was no significant relationship between with age or gender.

Discussion

One of the main aims of the TNM classification is to provide prognostic information that allows clinician to classify a newly diagnosed case of OTSCC at "low-risk," which will be managed by surgery only, or at "high-risk," which is prone to receive a treatment based on surgery associated with elective neck dissection and radiotherapy. The recently revised 8th edition of AJCC staging manual has incorporated the DOI in the T stage criteria, with the aim of increase the predictive power of TNM system. Here, we analyzed the effects of this modification in a large multicenter cohort of small (≤ 4 cm in diameter) OTSCC lesions with clinically negative neck. We found that many cases classified as T1 or T2 stage (early stage) according to the AJCC 7th become T3 (advanced stage) according to the AJCC 8th, and these T3 cases have a poor prognosis compared with T1–T2 cases.

This modification in the T category solved the drawback in many cases that had occurred when using the previously in staging of patients with small OTSCC with clinically negative neck. Recent studies have reported that such cases had a high rate of lymph node metastasis, recurrence, and cancer-related mortality [2, 3]. In our previous study covering all stages (I–IV) of OTSCC, stage II

Table 2 Survival analysis of 311 cases of small OTSCC (≤ 4 cm in diameter) with clinically negative neck according to the AJCC 7th edition, the AJCC 8th edition, and our proposal. In the multivariate analyses, T stage was entered into the model comprising age, gender, and WHO grade

| Variable	Number of cases (%)	Disease-specific survival		Disease-free survival	
		Univariate analysis HR (95% CI), P	Multivariate analysis HR (95% CI), P	Univariate analysis HR (95% CI), P	Multivariate analysis HR (95% CI), P
T stage (AJCC 7th)					
T1N0	124 (39.9)	1	1	1	1
T2N0	187 (60.1)	1.48 (0.87–2.54), $P = 0.15$	1.67 (0.97–2.89), $P = 0.08$	0.87 (0.57–1.33), $P = 0.53$	0.91 (0.59–1.40), $P = 0.67$
T stage (AJCC 8th)					
T1–2N0	291 (93.6)	1	1	1	1
T3	20 (6.4)	2.21 (1.05–4.64), $P = 0.036$	2.37 (1.12–4.99), $P = 0.023$	2.08 (1.07–4.01), $P = 0.03$	2.12 (1.09–4.08), $P = 0.027$
T stage (our proposal)					
T1–2N0	150 (48.2)	1	1	1	1
T3	161 (51.8)	3.87 (2.10–7.13), $P < 0.001$	4.19 (2.27–7.74), $P < 0.001$	1.55 (1.01–2.37), $P = 0.04$	1.62 (1.05–2.49), $P = 0.029$
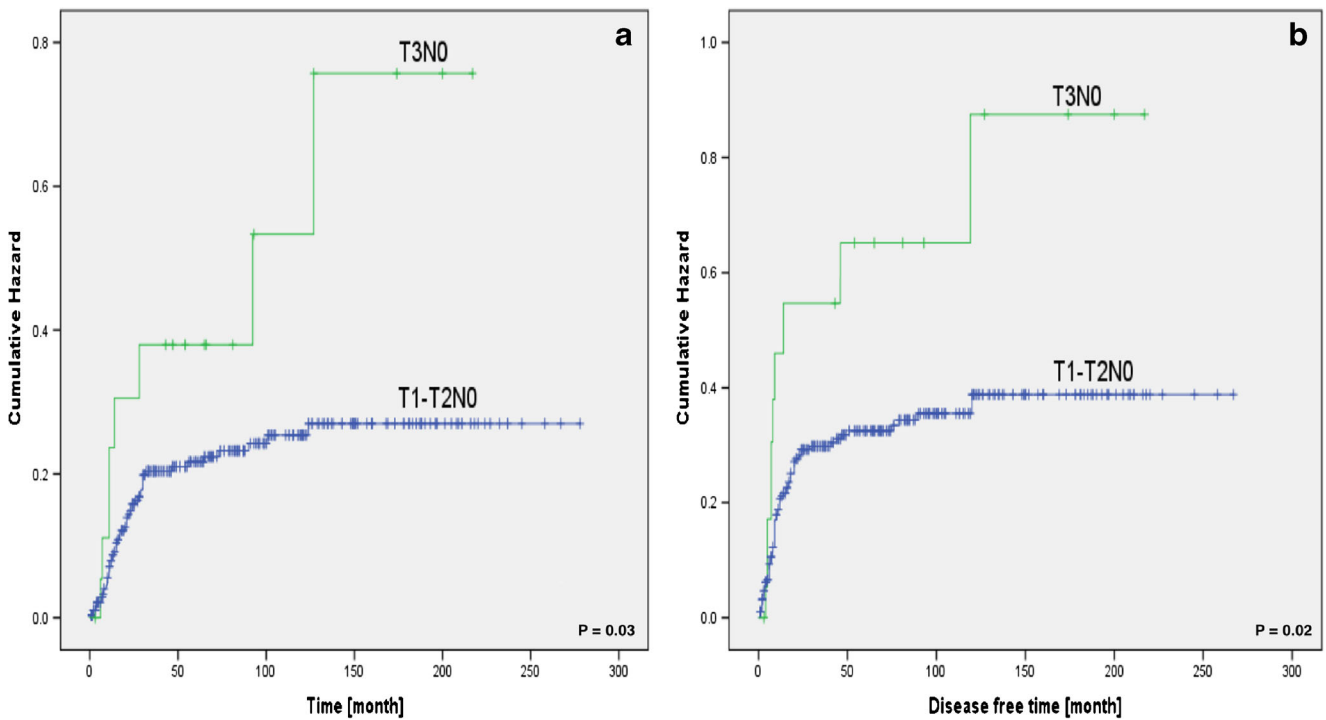
Fig. 1 Kaplan-Meier curves for DSS (**a**) and DFS (**b**) in small OTSCC according to AJCC 8th. DSS, disease-specific survival; DFS, disease-free survival

patients had a poor survival, which was almost similar to stage III patients [14]. This indicates understaging in some stage II cases according to the AJCC 7th [5]. In such cases, understaging would be solved by applying

the AJCC 8th, which incorporates DOI, and thus upstaging them from stage T1–T2 to T3.

The AJCC 8th applies a cutoff point of 5 mm DOI for upstaging from stage T1 to T2 and 10 mm for upstaging to
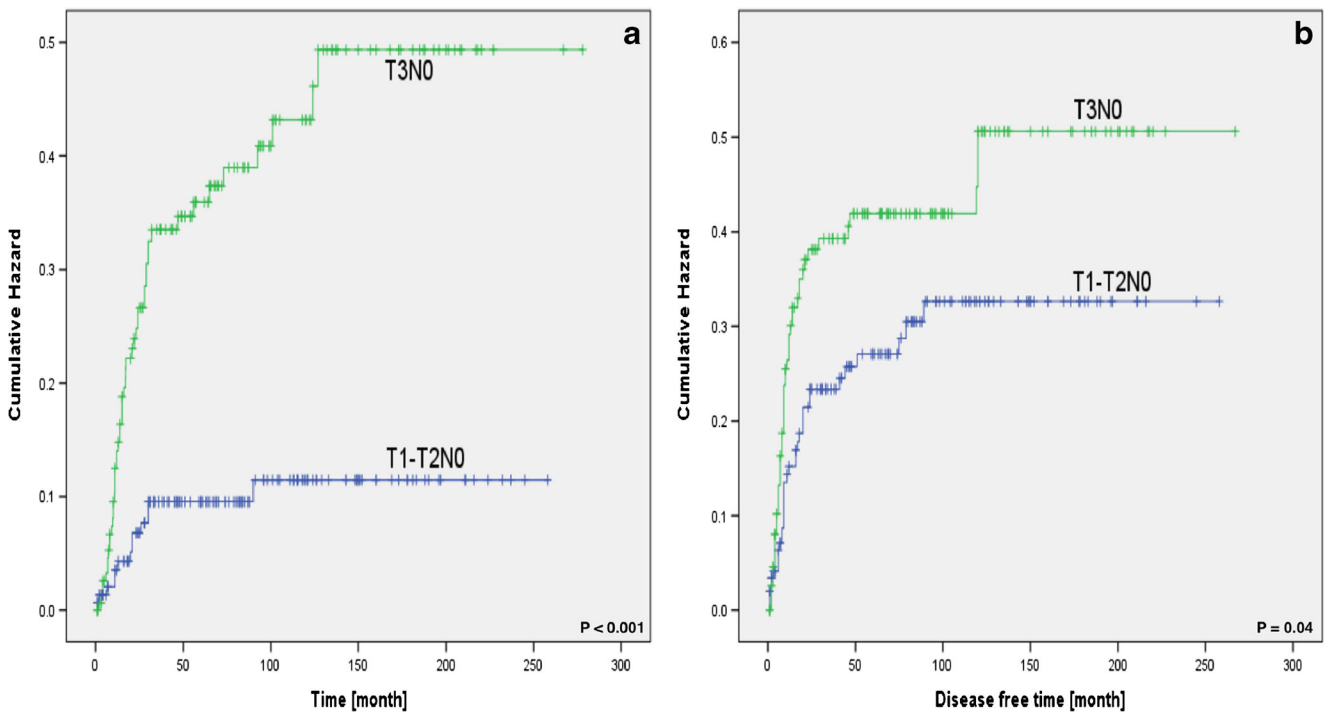
Fig. 2 Kaplan-Meier curves for DSS (**a**) and DFS (**b**) in small OTSCC according to our proposal. DSS, disease-specific survival; DFS, disease-free survival

Table 3 Summary of recent studies published during the last 10 years (2007–2017) and have evaluated the prognostic value of DOI in large cohorts (> 100 cases) of small OSCC with clinically negative lymph nodes

Authors, year	Country	Cases	Stage	Location	DOI cutoff point (mm)	Main finding about DOI
Melkane et al. [15], 2012	France	166	cT1–T2N0	OSCC	6.5	The sentinel node (SN) involvement was associated with DOI (median DOI for SN+ tumors was 6.5 mm).
					4	(median DOI for SN− tumors was 4 mm).
Ganly et al. [7], 2012	USA	216	cT1–T2N0	OTSCC	2	DOI is a prognostic factor for NRFS in multivariate analysis.
					4	DOI is associated with worse DSS and OS in univariate analysis.
Melchers et al. [16], 2012	Netherlands	212	pT1cN0	OSCC	4	DOI is an indicator to perform elective neck dissection.
Almangush et al. [3], 2015	Finland, Brazil and USA	479	cT1–T2N0	OTSCC	4	DOI is associated with DFS and DSS in multivariate analysis.
Xie et al. [13], 2015	China	106	cT1–T2N0	OTSCC	4	DOI was significantly associated with LN metastasis and OS.
Hakeem et al. [11], 2016	India	176	cT1–T2N0	OTSCC	5	DOI was associated with development of regional recurrence.
Wang et al. [9], 2017	China	144	cT1–T2N0	OSCC	2	DOI was not associated with OS in multivariate analysis.
Arora et al. [8], 2017	India	336	cT1–T2N0	OSCC	4	Patients with a DOI > 4 mm have a high risk of LN involvement.

DOI, depth of invasion; *DSS*, disease-specific survival; *DFS*, disease-free survival; *NRFS*, neck recurrence-free survival; *LN*, lymph node; *OSCC*, oral squamous cell carcinoma; *OTSCC*, oral tongue squamous cell carcinoma; *SN*, sentinel node; *OS*, overall survival

T3. However, this appears to be problematic as numerous cases of deeply invasive tumors (> 4 mm to 10 mm DOI) will remain in stage T1 or T2. It is noteworthy that deep invasion of > 4 mm carries a risk for locoregional metastasis and is associated with poor prognosis [3, 7, 8, 13, 15, 16]. Several recent studies (Table 3) have evaluated the prognostic value of DOI and reported consistent results with DOI being a promising prognosticator. Although the cutoff point has varied in these studies, a value of 4 mm is widely used. Of note, 4 mm has been also suggested as an optimal cutoff point in a meta-analysis of OSCC studies [12]. For this reason, we propose for future discussions regarding the development of the AJCC staging system that cases with invasive growth deeper than 4 mm should be considered for upstaging to advanced T category, i.e., stage T3.

The 8th edition of the AJCC manual states that DOI, not tumor thickness, must be used for T staging. However, a recent study has reported a similar performance whether using DOI or tumor thickness for T staging according to AJCC 8th [17]. Tumor thickness can be evaluated preoperatively by ultrasonography [18, 19] and magnetic resonance imaging [20–23]. On the other hand, it is sometimes difficult to assess DOI accurately using imaging [1]. In the histopathologic assessment, significant differences between the measurements of tumor thickness and DOI were noted in only a small number of cases [17]. In addition, agreement between histologic measurement and preoperative image measurement of tumor thickness has been reported in OTSCC [24]. Therefore, further research should evaluate the incorporation of tumor thickness as measured by preoperative imaging in the T staging. This

might be more useful for treatment planning than DOI, which is a histopathologic measurement and accurately assessed only postoperatively. Importantly, evaluation of DOI in preoperative biopsies requires truly representative samples, which is sometimes challenging [25].

In conclusion, the new criteria introduced in the AJCC 8th for T staging reclassified many T1–T2 OTSCCs with cN0 in our series to T3 (advanced stage), and such cases had a poor prognosis. The T stage criteria can be further optimized by considering any tumor > 4 cm in diameter and/or any tumor with DOI > 4 mm as T3 stage. Larger studies will be needed to further validate the prognostic value of OTSCC staging according to the AJCC 8th edition, and are also necessary to assess our proposal for re-staging using DOI of 4 mm for upstaging to T3.

Compliance with ethical standards

References

1. Glastonbury CM, Mukherji SK, O'Sullivan B, Lydiatt WM (2017) Setting the Stage for 2018: How the Changes in the American Joint Committee on Cancer/Union for International Cancer Control Cancer Staging Manual Eighth Edition Impact Radiologists. AJNR Am J Neuroradiol 38:2231–2237. https://doi.org/10.3174/ajnr.A5409

2. Rusthoven K, Ballonoff A, Raben D, Chen C (2008) Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. Cancer 112:345–351. https://doi.org/10.1002/cncr.23183

3. Almangush A, Bello IO, Coletta RD, Makitie AA, Makinen LK, Kauppila JH, Pukkila M, Hagstrom J, Laranne J, Soini Y, Kosma VM, Koivunen P, Kelner N, Kowalski LP, Grenman R, Leivo I, Laara E, Salo T (2015) For early-stage oral tongue cancer, depth of invasion and worst pattern of invasion are the strongest pathological predictors for locoregional recurrence and mortality. Virchows Arch 467: 39–46. https://doi.org/10.1007/s00428-015-1758-z

4. Piazza C, Montalto N, Paderno A, Taglietti V, Nicolai P (2014) Is it time to incorporate 'depth of infiltration' in the T staging of oral tongue and floor of mouth cancer? Curr Opin Otolaryngol Head Neck Surg 22:81–89. https://doi.org/10.1097/MOO.0000000000000038

5. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (eds) (2010) AJCC cancer staging manual, 7th edn. Springer, New York

6. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR (eds) (2017) AJCC cancer staging manual, 8th edn. Springer, New York

7. Ganly I, Patel S, Shah J (2012) Early stage squamous cell cancer of the oral tongue–clinicopathologic features affecting outcome. Cancer 118:101–111. https://doi.org/10.1002/cncr.26229

8. Arora A, Husain N, Bansal A, Neyaz A, Jaiswal R, Jain K, Chaturvedi A, Anand N, Malhotra K, Shukla S (2017) Development of a new outcome prediction model in early-stage squamous cell carcinoma of the oral cavity based on histopathologic parameters with multivariate analysis: the Aditi-Nuzhat Lymph-node Prediction Score (ANLPS) System. Am J Surg Pathol 41:950–960. https://doi.org/10.1097/PAS.0000000000000843

9. Wang S, Fan H, Xu J, Zhao E (2017) Prognostic implication of NOTCH1 in early stage oral squamous cell cancer with occult metastases. Clin Oral Investig 22:1131–1138. https://doi.org/10.1007/s00784-017-2197-9

10. Han MW, Lee JC, Kim YM, Cha HJ, Roh JL, Choi SH, Nam SY, Cho KJ, Kim SW, Kim SY (2015) Epithelial-mesenchymal transition: clinical implications for nodal metastasis and prognosis of tongue cancer. Otolaryngol Head Neck Surg 152:80–86. https://doi.org/10.1177/0194599814556061

11. Hakeem AH, Pradhan SA, Kannan R, Tubachi J (2016) Clinical outcome of surgical treatment of T1-2 N0 squamous cell carcinoma of oral tongue with observation for the neck: analysis of 176 cases. Ann Maxillofac Surg 6:235–240. https://doi.org/10.4103/2231-0746.200331

12. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B (2009) Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. Cancer 115:1489–1497. https://doi.org/10.1002/cncr.24161

13. Xie N, Wang C, Liu X, Li R, Hou J, Chen X, Huang H (2015) Tumor budding correlates with occult cervical lymph node metastasis and poor prognosis in clinical early-stage tongue squamous cell carcinoma. J Oral Pathol Med 44:266–272. https://doi.org/10.1111/jop.12242

14. Mroueh R, Haapaniemi A, Grenman R, Laranne J, Pukkila M, Almangush A, Salo T, Makitie A (2017) Improved outcomes with oral tongue squamous cell carcinoma in Finland. Head Neck 39: 1306–1312. https://doi.org/10.1002/hed.24744

15. Melkane AE, Mamelle G, Wycisk G, Temam S, Janot F, Casiraghi O, Lumbroso J (2012) Sentinel node biopsy in early oral squamous cell carcinomas: a 10-year experience. Laryngoscope 122:1782–1788. https://doi.org/10.1002/lary.23383

16. 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 48:337–342. https://doi.org/10.1016/j.oraloncology.2011.11.007

17. Dirven R, Ebrahimi A, Moeckelmann N, Palme CE, Gupta R, Clark J (2017) Tumor thickness versus depth of invasion - analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. Oral Oncol 74:30–33. https://doi.org/10.1016/j.oraloncology.2017.09.007

18. Mark Taylor S, Drover C, Maceachern R, Bullock M, Hart R, Psooy B, Trites J (2010) Is preoperative ultrasonography accurate in measuring tumor thickness and predicting the incidence of cervical metastasis in oral cancer? Oral Oncol 46:38–41. https://doi.org/10.1016/j.oraloncology.2009.10.005

19. Lodder WL, Teertstra HJ, Tan IB, Pameijer FA, Smeele LE, van Velthuysen ML, van den Brekel MW (2011) Tumour thickness in oral cancer using an intra-oral ultrasound probe. Eur Radiol 21:98–106. https://doi.org/10.1007/s00330-010-1891-7

20. Iwai H, Kyomoto R, Ha-Kawa SK, Lee S, Yamashita T (2002) Magnetic resonance determination of tumor thickness as predictive factor of cervical metastasis in oral tongue carcinoma. Laryngoscope 112:457–461. https://doi.org/10.1097/00005537-200203000-00010

21. Preda L, Chiesa F, Calabrese L, Latronico A, Bruschini R, Leon ME, Renne G, Bellomi M (2006) Relationship between histologic thickness of tongue carcinoma and thickness estimated from preoperative MRI. Eur Radiol 16:2242–2248. https://doi.org/10.1007/s00330-006-0263-9

22. Okura M, Iida S, Aikawa T, Adachi T, Yoshimura N, Yamada T, Kogo M (2008) Tumor thickness and paralingual distance of coronal MR imaging predicts cervical node metastases in oral tongue carcinoma. AJNR Am J Neuroradiol 29:45–50. https://doi.org/10.3174/ajnr.A0749

23. Jung J, Cho NH, Kim J, Choi EC, Lee SY, Byeon HK, Park YM, Yang WS, Kim SH (2009) Significant invasion depth of early oral tongue cancer originated from the lateral border to predict regional metastases and prognosis. Int J Oral Maxillofac Surg 38:653–660. https://doi.org/10.1016/j.ijom.2009.01.004

24. Madana J, Laliberte F, Morand GB, Yolmo D, Black MJ, Mlynarek AM, Hier MP (2015) Computerized tomography based tumor-thickness measurement is useful to predict postoperative pathological tumor thickness in oral tongue squamous cell carcinoma. J Otolaryngol Head Neck Surg 44:49. https://doi.org/10.1186/s40463-015-0089-z

25. Almangush A, Leivo I, Siponen M, Sundquist E, Mroueh R, Makitie AA, Soini Y, Haglund C, Nieminen P, Salo T (2017) Evaluation of the budding and depth of invasion (BD) model in oral tongue cancer biopsies. Virchows Arch 472:231–236. https://doi.org/10.1007/s00428-017-2212-1