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Tumor Depth of Invasion (Tumor > 4 cm/Depth > 10 mm and Depth > 20 mm) and Through Cortex/Skin Invasion are Both Valid Criteria for Classifying Tumors as pT4a in AJCC 2018 Oral Cavity Cancer Staging System

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ABSTRACT

Background. According to the AJCC third to seventh edition staging manuals (1988–2010), the presence of through cortex and/or skin invasion in oral cavity squamous cell carcinoma (OCSCC) identifies T4a tumors. The AJCC eighth edition (2018) introduced a depth of invasion (DOI) > 20 mm as a criterion for pT4a. Subsequently, a revision maintained that tumors > 4 cm with a DOI > 10 mm should be classified as pT4a. We sought to analyze the prognostic impact of the three distinct criteria identifying pT4a disease.

Methods. We examined 667 consecutive patients with pT3-4 buccal/gum/hard palate/retromolar SCC who underwent surgery between 1996 and 2016. pT1/pT2 (n = 108/359) disease were included for comparison purposes.

Results. The 5-year outcomes of patients with pT1/pT2/without (n = 406)/with tumor > 4 cm/DOI > 10 mm (n = 261), pT1/pT2/DOI ≤ 20 mm (n = 510)/> 20 mm (n = 157), and pT1/pT2/without (n = 305)/with through cortex/skin invasion (n = 362) were as follows: disease-specific survival (DSS), 98%/89%/79%/65%, $p < 0.001$, 98%/89%/78%/59%, $p < 0.001$, and 98%/89%79%/69%, $p < 0.001$; overall survival (OS), 90%/79%/63%/51%, $p < 0.001$, 90%/79%/63%/42%, $p < 0.001$, and 90%/79%/65%/52%, $p < 0.001$. In pT3-4 disease, a tumor > 4 cm/DOI > 10 mm was an independent adverse prognosticator for 5-year DSS rate, DOI > 20 mm was an independent adverse prognosticator for 5-year DSS and OS rates,

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whereas through cortex/skin invasion independently predicted 5-year OS rates.

Conclusions. All of the three criteria (tumor > 4 cm/DOI > 10 mm, DOI > 20 mm, and through cortex/skin invasion) identify high-risk patients, which should be reflected in further revisions of pT4a classification in OCSCC.

Compared with the previous third to seventh editions (1988–2010), the eight edition (2017) of the American Joint Committee on Cancer (AJCC) Staging Manual has been updated with the goal of maximizing its utility for clinical research and prognostic stratification.[1] Major changes for oral cavity squamous cell carcinoma (OCSCC) were as follows: (1) the presence of a depth of invasion (DOI) > 5 mm but ≤ 10 mm leads to a disease upstaging to T2; (2) the presence of a DOI > 10 mm leads to a disease upstaging to T3; and (3) the presence of a DOI > 20 mm identifies T4a status (a criterion introduced in the first 2018 update).[2] Notably, the second 2018 update maintained that the presence of tumor > 4 cm with a DOI > 10 mm should lead to a pT4a classification, whereas a DOI > 20 mm did not longer identify a T4a tumor. In addition to this newly defined criterion, the AJCC third to seventh edition staging manuals indicated that tumors showing through cortex (at the mandible, maxilla, or maxillary sinus) and/or skin invasion should be considered as T4a (Fig. 1).

The reasons to upstage T2-3 tumors according to DOI are to be found in the results of a large international collaborative study, which was nonetheless limited by the lack of specific data on T4 tumors.[3] Notably, the authors were unable to determine how many patients were staged as pT4 based on DOI versus other criteria (e.g., evidence of extrinsic muscle invasion or through cortex/skin invasion).[3] Another point that merits consideration is that tongue SCC is the most frequent oral cavity malignancy in countries where betel quid chewing is uncommon. In contrast, most patients with OCSCC in betel quid chewing endemic areas are diagnosed with buccal, gum, hard palate, and retromolar trigone neoplasms. Moreover, survival data in support of tumor > 4 cm/DOI > 10 mm or DOI > 20 mm as criteria to classify a tumor as T4a have not yet been

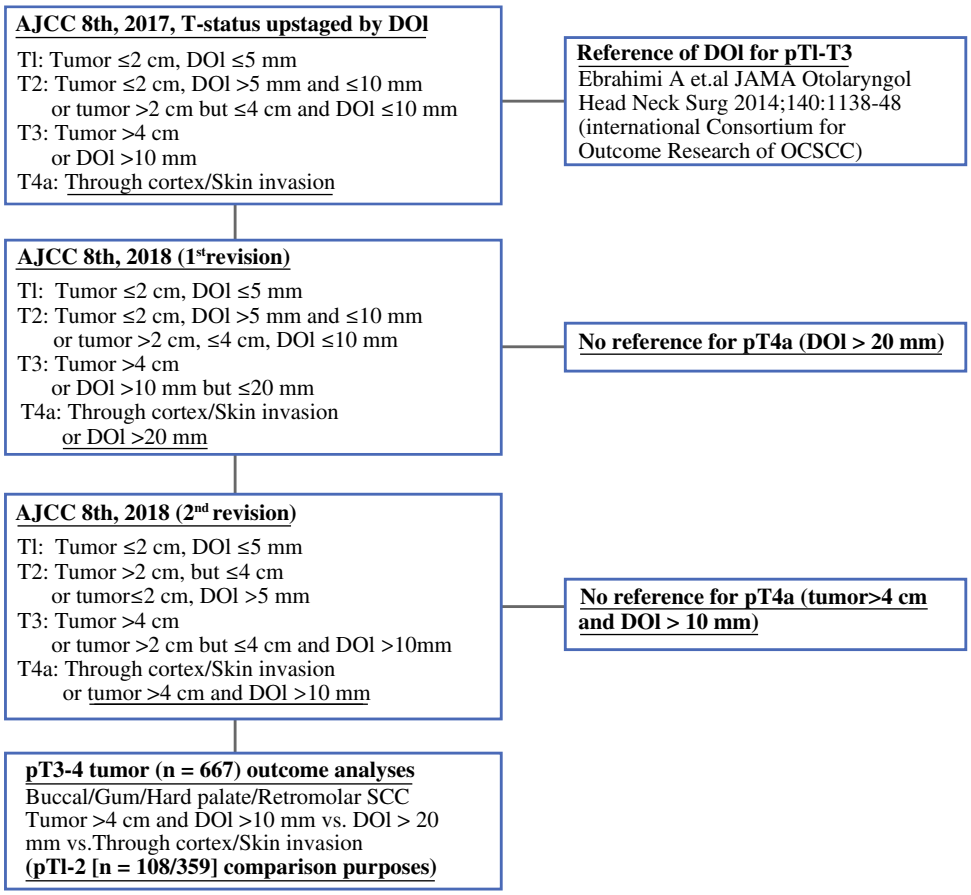

FIG. 1 Flow of patients through the study

published. To address this knowledge gap, we designed the current retrospective study of prospectively collected data in a large cohort of patients with pT3-4 buccal/gum/hard palate/retromolar SCC from a betel quid chewing endemic area. We initially investigated the optimal cutoff values for pathological DOI in relation to clinical outcomes of patients with pT3-4 disease. We subsequently analyzed the prognostic impact of the three criteria identifying pT4a disease (tumor > 4 cm/DOI > 10 mm [AJCC 2018, second revision], DOI > 20 mm [AJCC 2018, first revision] according to the AJCC eight edition staging manual; through cortex/skin invasion according to the AJCC seventh edition staging manual). To further investigate the discriminatory capacity of T classification according to the three criteria identifying pT4a tumors, patients with pT1-2 disease also were included for comparison purposes.[4]

PATIENTS AND METHODS

Study Subjects

This study was designed as a retrospective analysis of prospectively collected data. Consequently, data on DOI and other variables of interest were collected in a blinded fashion with respect to the study end points. We reviewed the clinical records of consecutive patients with pT3-4 buccal/gum/hard palate/retromolar SCC (n = 667, according to the AJCC 2018 second revision criteria) who underwent surgery between January 1996 and November 2016. The application of the AJCC 2018 staging manual (i.e., after the introduction of a tumor > 4 cm and DOI > 10 mm and the exclusion of DOI > 20 mm as criteria for T4a) led to the following pT classification: 191 (28.6%) pT3 tumors and 476 (71.4%) pT4 tumors. We then analyzed the prognostic impact of the three criteria identifying pT4a disease. To this aim, patients were divided into the following groups: without a tumor > 4 cm/DOI > 10 mm (n = 406) versus with tumor > 4 cm/DOI > 10 mm (n = 261), presence a DOI ≤ 20 mm (n = 510) versus > 20 mm (n = 157), and absence of through cortex (i.e., at the mandible, maxilla, or maxillary sinus)/skin invasion (n = 305) versus its presence (n = 362). Patients seen in the same study period and harboring pT1/pT2 (n = 108/359) disease were included for comparison purposes. Details on the presurgical evaluation and staging workup have been previously described.[5–9] Ethical approval was granted by the local Institutional Review Board (CGMH 101-4457B). Due to the retrospective nature of the study, the need for informed consent was waived.

Surgery and Adjuvant Therapy

Primary tumors were excised with ≥ 1-cm safety margins (both peripheral and deep margins). Patients with cN + disease were treated with level I–V neck dissections (NDs), whereas cN- patients underwent level I–III NDs. We offered postoperative radiotherapy (RT, 60 Gy) to patients bearing pathological risk factors (RFs). RFs were classified in accordance with the National Comprehensive Cancer Network (NCCN) guidelines before 2008.[10] Subsequently, the CGMH guidelines were implemented as described in our previous publications. RT was administered to patients who carried the following RFs: pT4, pT3N1, or pT1-2N1 disease (pN1 disease at level IV/V); 1–2 mm close margins (when a second surgical operation was unfeasible); and poor differentiation with a DOI ≥ 4 mm. RT was also offered to patients who harbored two minor RFs (i.e., pN1, DOI ≥ 10 mm, 3–4 mm close margins, poor differentiation, perineural invasion, lymphatic invasion, and vascular invasion).[9] The radiation field included both the entire tumor bed area (with 1–2 cm margins) and regional lymphatics. Concomitant chemoradiotherapy (CCRT, 66 Gy) was used to treat patients showing extranodal extension (ENE), multiple lymph node metastases, or positive margins (when a second surgical operation was unfeasible). CCRT was also administered to patients carrying at least three of the above-mentioned minor RFs (pT4 and 1–4 mm close margins were considered as one RF for the purpose of CCRT).[11–13] The chemotherapy regimen consisted of intravenous cisplatin 50 mg/m^2 biweekly plus daily oral tegafur 800 mg and leucovorin 60 mg, cisplatin 40 mg/m^2 weekly, or cisplatin 100 mg/m^2 every 3 weeks.[13]

Determination of the Optimal Cutoff Values for Pathological DOI in pT3-4 Disease

The optimal cutoff values for tumor depth in pT3-4 disease were calculated as previously described.[5–8] In brief, different values of tumor depth (1–30 mm) were tested using the Kaplan–Meier method based on 5-year, disease-specific survival (DSS) and overall survival (OS). A cutoff point of 20 mm (> 20 mm vs. ≤ 20 mm) yielded the highest significance in terms of survival rates, in keeping with the value proposed by the first revision of AJCC eight edition (2018) staging manual.

Statistical Analysis

Follow-up visits were continued until November 2018. All of the patients received follow-up examinations for at least 24 months or until death. Descriptive statistics are summarized as frequencies, percentages, means, medians,

ranges, and standard deviations (SDs). The 5-year DSS and OS rates served as the main outcome measures. Survival curves were plotted with the Kaplan–Meier method (log-rank test). Univariate and multivariate Cox proportional hazards regression analyses with a forward selection procedure were used to identify the independent predictors of survival endpoints. In patients with pT3-4 disease, a total of 17 covariates (tumor > 4 cm and DOI > 10 mm, DOI [cutoff: 20 mm], through cortex/skin invasion, sex, age, preoperative alcohol drinking, betel quid chewing, cigarette smoking, pN, ENE, contralateral neck nodal metastases, tumor differentiation, margin status, perineural invasion, lymphatic invasion, vascular invasion, and treatment modality) were entered into univariate and multivariate models. The proportional hazards assumption was tested and confirmed for each Cox regression model (Supplement Fig. 1). Subjects with missing values (regardless of the variable) were excluded from the analysis. Two-tailed p values < 0.05 were considered statistically significant.

RESULTS

Patients

Table 1 summarizes the general characteristics of patients with pT3-4 disease. Compared with patients without tumor > 4 cm/DOI > 10 mm, those with tumor > 4 cm/DOI > 10 mm had a higher likelihood of having preoperative betel quid chewing, bilateral NDs, ENE, margin status of ≤ 4 mm, perineural invasion, and adjuvant CCRT. Compared with patients with a DOI ≤ 20 mm, those with a DOI > 20 mm had a higher likelihood of having preoperative betel quid chewing, bilateral NDs, pN3b disease, ENE, margin status ≤ 4 mm, perineural invasion, and adjuvant CCRT. Compared with patients without evidence of through cortex/skin invasion, those who showed through cortex/skin invasion had a higher likelihood of having bilateral NDs, ENE, pN2c, perineural invasion, lymphatic invasion, and adjuvant CCRT. Compared with patients who had tumor > 4 cm/DOI > 10 mm and through cortex/skin invasion, those with DOI > 20 mm had the highest frequency of preoperative betel quid chewing (93.0% vs. 91.2%, 86.5%, respectively), bilateral NDs (17.3% vs. 15.1%, 14.2%, respectively), pN3b disease (33.3% vs. 29.0%, 27.7%, respectively), ENE (37.8% vs. 35.5%, 33.0%, respectively), margin status ≤ 4 mm (19.5% vs. 19.2%, 15.9%, respectively), perineural invasion (43.9% vs. 42.5%, 39.5%, respectively), and CCRT (45.2% vs. 39.1%, 37.6%, respectively).

Five-Year Outcomes

The median follow-up time in the entire study cohort was 72 months (mean: 82 months; standard deviation [SD]: 62 months; range: 1–261 months), whereas the median follow-up in the subgroup of patients who survived was 108 months (mean: 113 months; SD: 57 months; range: 24–261 months). The 5-year outcomes of patients with pT1-4 disease were as follows: DSS, 81% (pT3-4: 74%) and OS, 68% (pT3-4: 58%) respectively. The following 5-year DSS were observed in patients with pT1/pT2/pT3-4 disease (without a tumor > 4 cm/DOI > 10 mm [vs. with], DOI ≤ 20 mm [vs. > 20 mm] and without through cortex/skin invasion [vs. with]): 98%/89%/79%/65%, $p < 0.001$ (without vs. with tumor > 4 cm/DOI > 10 mm, $p < 0.001$), 98%/89%/78%/59%, $p < 0.001$ (DOI ≤ 20 mm vs. > 20 mm, $p < 0.001$), and 98%/89%/79%/69%, $p < 0.001$ (without vs. those with through cortex/skin invasion, $p = 0.005$), respectively (Fig. 2a–c). The following 5-year OS were observed in patients with pT1/pT2/pT3-4 disease (without tumor > 4 cm/DOI > 10 mm [vs. with], DOI ≤ 20 mm [vs. > 20 mm] and without through cortex/skin invasion [vs. *with*]) 90%/79%/63%/51%, $p < 0.001$ (without vs. with a tumor > 4 cm/DOI > 10 mm, $p = 0.001$), 90%/79%/63%/42%, $p < 0.001$ (DOI ≤ 20 mm vs. > 20 mm, $p < 0.001$), and 90%/79%/65%/52%, $p < 0.001$ (without vs. those with through cortex/skin invasion, $p < 0.001$; Fig. 2d–f).

Univariate and Multivariate Analyses of 5-Year Outcomes in Patients with pT3-4 Disease

The results of univariate analysis for 5-year DSS, and OS rates in patients with pT3-4 disease are summarized in Table 2, whereas Table 3 shows the results of multivariate analysis (MVA). Besides tumor > 4 cm/DOI > 10 mm, DOI > 20 mm, and the presence of through cortex/skin invasion, the following variables were identified as significant predictors of DSS and OS: pN2-3b disease, ENE, contralateral neck nodal metastases, poor differentiation, perineural invasion, lymphatic invasion, and vascular invasion (Table 2). The results of MVA identified a tumor > 4 cm/DOI > 10 mm as an independent adverse prognosticator for 5-year DSS. A DOI > 20 mm was identified as an independent adverse prognosticator for 5-year DSS and OS rates. In contrast, the presence of through cortex/skin invasion independently predicted 5-year OS rates.

TABLE 1 General characteristics of pT3-4 patients with buccal, gum, hard palate, and retromolar squamous cell carcinoma (n = 667)

Characteristic (n, %)	Without tumor > 4 cm and DOI > 10 mm (n = 406) n (%)	With tumor > 4 cm and DOI > 10 mm (n = 261) n (%)	p	DOI ≤ 20 mm (n = 510) n (%)	DOI > 20 mm (n = 157) n (%)	p	Without through cortex/skin invasion (n = 305) n (%)	With through cortex/skin invasion (n = 362) n (%)	p
DOI			< 0.001						< 0.001
≤ 20 mm (510, 76.5)	367 (90.4)	143 (54.8)					271 (88.9)	239 (66.0)	
> 20 mm (157, 23.5)	39 (9.6)	118 (45.2)					34 (11.1)	123 (34.0)	
Sex			0.165			0.164			0.130
Male (640, 96.0)	386 (95.1)	254 (97.3)		486 (95.3)	154 (98.1)		296 (97.0)	344 (95.0)	
Female (27, 4.0)	20 (4.9)	7 (2.7)		24 (4.7)	3 (1.9)		9 (3.0)	18 (5.0)	
Age of disease onset, years			0.174			0.434			0.657
< 65 (572, 85.8)	342 (84.2)	230 (88.1)		434 (85.1)	138 (87.9)		264 (86.6)	308 (85.1)	
≥ 65 (95, 14.2)	64 (15.8)	31 (11.9)		76 (14.9)	19 (12.1)		41 (13.4)	54 (14.9)	
Preoperative alcohol drinking			0.074			0.096			0.045
No (211, 31.6)	139 (34.2)	72 (27.6)		170 (33.3)	41 (26.1)		84 (27.5)	127 (35.1)	
Yes (456, 68.4)	267 (65.8)	189 (72.4)		340 (66.7)	116 (73.9)		221 (72.5)	235 (64.9)	
Preoperative betel quid chewing			0.017			0.013			0.561
No (85, 12.7)	62 (15.3)	23 (8.8)		74 (14.5)	11 (7.0)		36 (11.8)	49 (13.5)	
Yes (582, 87.3)	344 (84.7)	238 (91.2)		436 (85.5)	146 (93.0)		269 (88.2)	313 (86.5)	
Preoperative cigarette smoking			0.817			0.596			0.821
No (90, 13.5)	56 (13.8)	34 (13.0)		71 (13.9)	19 (12.1)		40 (13.1)	50 (13.8)	
Yes (577, 86.5)	350 (86.2)	227 (87.0)		439 (86.1)	138 (87.9)		265 (86.9)	312 (86.2)	
Bilateral neck dissection			0.004			0.003			0.001
No (583, 89.4)	363 (92.4)	220 (84.9)		454 (91.5)	129 (82.7)		276 (93.9)	307 (85.8)	
Yes (69, 10.6)	30 (7.6)	39 (15.1)		42 (8.5)	27 (17.3)		18 (6.1)	51 (14.2)	
Pathological N status[a]			0.116			0.023			0.086
pN0 (344, 52.8)	219 (55.7)	125 (48.3)		275 (55.4)	69 (44.2)		160 (54.4)	184 (51.4)	
pN1 (68, 10.4)	43 (10.9)	25 (9.7)		52 (10.5)	16 (10.3)		31 (10.5)	37 (10.3)	
pN2 (82, 12.6)	48 (12.2)	34 (13.1)		63 (12.7)	19 (12.2)		44 (15.0)	38 (10.6)	
pN3b (158, 24.2)	83 (21.1)	75 (29.0)		106 (21.4)	52 (33.3)		59 (20.1)	99 (27.7)	
Extranodal extension[a]			0.007			0.012			0.038
No (459, 70.5)	292 (74.5)	167 (64.5)		362 (73.1)	97 (62.2)		219 (74.7)	240 (67.0)	
Yes (192, 29.5)	100 (25.5)	92 (35.5)		133 (26.9)	59 (37.8)		74 (25.3)	118 (33.0)	

TABLE 1 continued

Characteristic (*n*, %)	Without tumor > 4 cm and DOI > 10 mm (*n* = 406) *n* (%)	With tumor > 4 cm and DOI > 10 mm (*n* = 261) *n* (%)	*p*	DOI ≤ 20 mm (*n* = 510) *n* (%)	DOI > 20 mm (*n* = 157) *n* (%)	*p*	Without through cortex/skin invasion (*n* = 305) *n* (%)	With through cortex/skin invasion (*n* = 362) *n* (%)	*p*
Contralateral pN+[a]			1.000			0.180			< 0.001
No (633, 97.1)	381 (96.9)	252 (97.3)		484 (97.6)	149 (95.5)		294 (100.0)	339 (94.7)	
Yes (19, 2.9)	12 (3.1)	7 (2.7)		12 (2.4)	7 (4.5)		0 (0.0)	19 (5.3)	
Differentiation			0.896			0.767			0.527
Well/moderate (598, 89.7)	363 (89.4)	235 (90.0)		456 (89.4)	142 (90.4)		276 (90.5)	322 (89.0)	
Poor (69, 10.3)	43 (10.6)	26 (10.0)		54 (10.6)	15 (9.6)		29 (9.5)	40 (11.0)	
Margin status[b]			0.004			0.034			0.178
≤ 4 mm (93, 14.1)	44 (10.9)	49 (19.2)		63 (12.5)	30 (19.5)		36 (12.0)	57 (15.9)	
> 4 mm (565, 85.9)	359 (89.1)	206 (80.8)		441 (87.5)	124 (80.5)		264 (88.0)	301 (84.1)	
Perineural invasion			0.006			0.023			0.052
No (426, 63.9)	276 (68.0)	150 (57.5)		338 (66.3)	88 (56.1)		207 (67.9)	219 (60.5)	
Yes (241, 36.1)	130 (32.0)	111 (42.5)		172 (33.7)	69 (43.9)		98 (32.1)	143 (39.5)	
Lymphatic invasion			0.879			0.111			< 0.001
No (619, 92.8)	376 (92.6)	243 (93.1)		478 (93.7)	141 (89.8)		295 (96.7)	324 (89.5)	
Yes (48, 7.2)	30 (7.4)	18 (6.9)		32 (6.3)	16 (10.2)		10 (3.3)	38 (10.5)	
Vascular invasion			0.678			0.337			0.219
No (642, 96.3)	392 (96.6)	250 (95.8)		493 (96.7)	149 (94.9)		297 (97.4)	345 (95.3)	
Yes (25, 3.7)	14 (3.4)	11 (4.2)		17 (3.3)	8 (5.1)		8 (2.6)	17 (4.7)	
Treatment modality			0.001			< 0.001			< 0.001
OP alone (160, 24.0)	116 (28.6)	44 (16.9)		139 (27.3)	21 (13.4)		113 (37.0)	47 (13.0)	
OP + RT (286, 42.9)	171 (42.1)	115 (44.1)		221 (43.3)	65 (41.4)		107 (35.1)	179 (49.4)	
OP + CCRT (221, 33.1)	119 (29.3)	102 (39.1)		150 (29.4)	71 (45.2)		85 (27.9)	136 (37.6)	

DOI depth of invasion (defined as the measured thickness from the surface of the normal mucosa to the deepest portion of the tumor), *OP* operation, *RT* radiotherapy, *CCRT* concurrent chemoradiotherapy

[a]Unavailable data: pN status (no neck dissection, *n* = 15)

[b]Unknown data: margin status (*n* = 9)

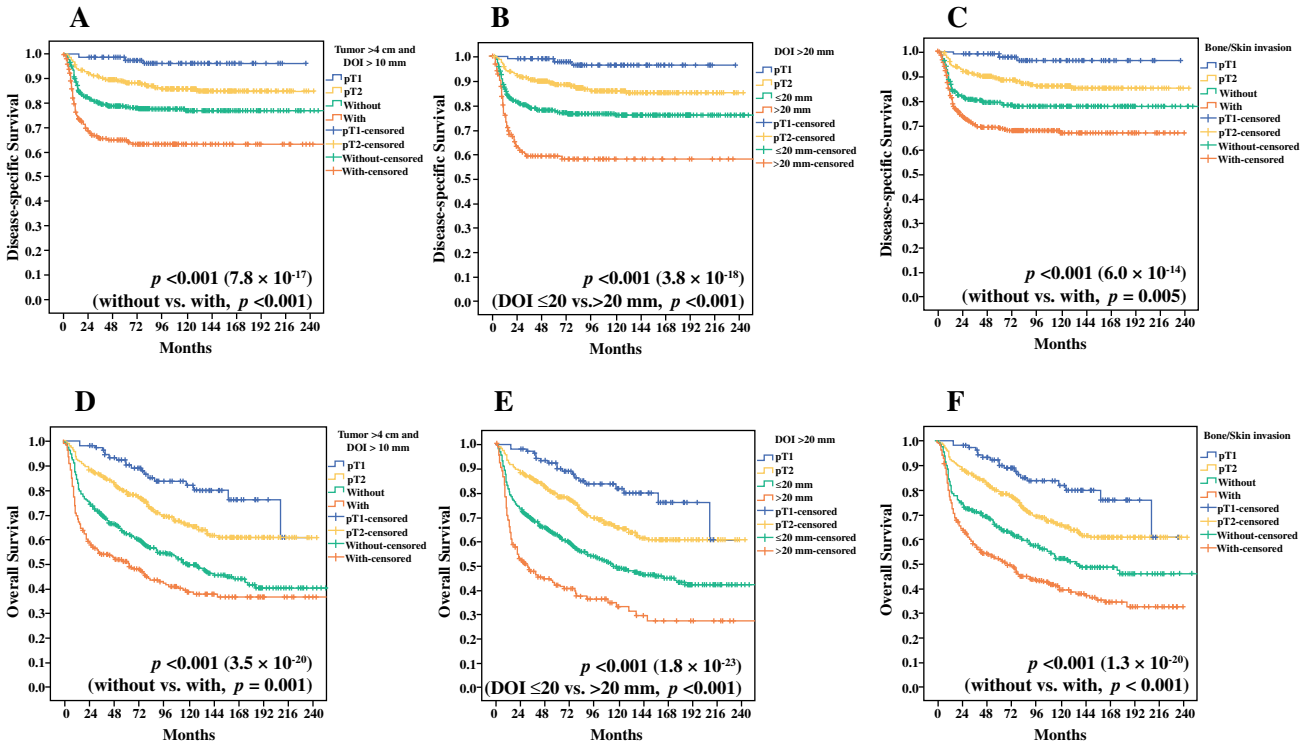

FIG. 2 Kaplan-Meier plots of 5-year, disease-specific survival and overall survival in patients with pT1-4 buccal/gum/hard palate/retromolar cancer stratified according to the presence (vs. absence) of tumor > 4 cm and depth of invasion > 10 mm (**a**, **d**), depth of invasion > 20 mm (vs. ≤ 20 mm) (**b**, **e**), and presence (vs. absence) of through cortex/skin invasion (**c**, **f**)

Discriminatory Capability of T Classification According to the Three Criteria Identifying pT4a Tumors

Although the p values for pT1-4 disease were all < 0.001 for 5-year DSS and OS according to the three criteria identifying pT4a disease, the detailed p values were as follows: DSS, $p = 7.8 \times 10^{-17}$ (Fig. 2a, criterion: tumor > 4 cm/DOI > 10 mm), $p = 3.8 \times 10^{-18}$ (Fig. 2b, criterion: DOI > 20 mm), and $p = 6.0 \times 10^{-14}$ (Fig. 2c, criterion: through cortex/skin invasion); OS, $p = 3.5 \times 10^{-20}$ (Fig. 2d, criterion: tumor > 4 cm/DOI > 10 mm), $p = 1.8 \times 10^{-23}$ (Fig. 2e, criterion: DOI > 20 mm), and $p = 1.3 \times 10^{-20}$ (Fig. 2f, criterion: through cortex/skin invasion). The T classification of pT1/pT2/DOI ≤ 20 mm/> 20 mm showed the highest discriminatory capability.

DISCUSSION

Buccal, gum, hard palate, and retromolar trigone malignancies are the most common form of OCSCC in betel quid chewing endemic areas. These neoplasms have a high tendency to spread through the cortical bone (i.e., reaching the marrow) and/or facial skin. We have previously shown that buccal SCC has a higher tendency toward distant metastases compared with tongue SCC.[14] Although through cortex/skin invasion is a criterion for T4a tumors, it is conceivable that the DOI may influence prognosis as well. Based on the findings by Piazza et al., the first update of 2018 AJCC eight edition staging manual maintained that the presence of a DOI > 20 mm identifies T4a status.[15] Of note, the eight edition introduced tumor > 4 cm and a DOI > 10 mm as a new criterion for classifying tumors as pT4a. Three caveats inherent in this new criterion merit comment. First, DOI data are not invariably present in all pathological reports of other head and neck teams, making the transition between different staging systems potentially problematic. Second, patients with pT4 OCSCC should at least receive adjuvant RT according to NCCN treatment guidelines. However, it is reasonable to hypothesize that most patients diagnosed with a DOI > 20 mm or tumor > 4 cm/DOI > 10 mm before the implementation of the AJCC eight edition staging manual would not have received such adjuvant therapies. Consequently, a concern exists that the proposed staging revision would lead to an unnecessary use of adjuvant therapies. Third, the impact of DOI > 20 mm or tumor > 4 cm/DOI > 10 mm remains unclear. All of these controversial points prompted us to conduct the current

TABLE 2 Five-year rates of disease-specific survival and overall survival in pT3-4 patients with buccal, gum, hard palate, and retromolar squamous cell carcinoma (n = 667)

Characteristics (n, %)	5-year disease-specific survival % (n event)	p	5-year overall survival % (n event)	p
Tumor > 4 cm and DOI > 10 mm		< 0.001		0.001
Without (406, 60.9)	79 (81)		63 (148)	
With (261, 39.1)	65 (83)		51 (126)	
DOI		< 0.001		< 0.001
≤ 20 mm (510, 76.5)	78 (106)		63 (186)	
> 20 mm (157, 23.5)	59 (58)		42 (88)	
Through cortex/skin invasion		0.005		< 0.001
Without (305, 45.7)	79 (60)		65 (104)	
With (362, 54.3)	69 (104)		52 (170)	
Sex		0.576		0.259
Male (640, 96.0)	74 (156)		58 (261)	
Female (27, 4.0)	65 (8)		48 (13)	
Age of disease onset, years		0.227		0.205
< 65 (572, 85.8)	73 (147)		59 (232)	
≥ 65 (95, 14.2)	80 (17)		54 (42)	
Preoperative alcohol drinking		0.005		0.241
No (211, 31.6)	82 (35)		64 (75)	
Yes (456, 68.4)	70 (129)		55 (199)	
Preoperative betel quid chewing		0.052		0.709
No (85, 12.7)	83 (13)		57 (35)	
Yes (582, 87.3)	72 (151)		58 (239)	
Preoperative cigarette smoking		0.256		0.971
No (90, 13.5)	78 (17)		59 (35)	
Yes (577, 86.5)	73 (147)		58 (239)	
Pathological N status[a]		< 0.001		< 0.001
pN0-1 (412, 63.2)	87 (49)		72 (112)	
pN2-3b (240, 36.8)	48 (112)		33 (157)	
Extranodal extension[a]		< 0.001		< 0.001
No (459, 70.5)	85 (67)		69 (138)	
Yes (192, 29.5)	44 (94)		31 (131)	
Contralateral pN+[a]		0.001		< 0.001
No (633, 97.1)	74 (151)		59 (254)	
Yes (19, 2.9)	39 (10)		21 (15)	
Differentiation		< 0.001		< 0.001
Well/moderate (598, 89.7)	76 (135)		60 (233)	
Poor (69, 10.3)	53 (29)		40 (41)	
Margin status[b]		0.042		0.112
≤ 4 mm (93, 14.1)	65 (30)		49 (45)	
> 4 mm (565, 85.9)	76 (125)		60 (220)	
Perineural invasion		< 0.001		< 0.001
No (426, 63.9)	81 (76)		64 (149)	
Yes (241, 36.1)	60 (88)		47 (125)	
Lymphatic invasion		< 0.001		< 0.001
No (619, 92.8)	76 (140)		61 (238)	
Yes (48, 7.2)	37 (24)		25 (36)	
Vascular invasion		0.001		0.032
No (642, 96.3)	75 (152)		59 (259)	
Yes (25, 3.7)	47 (12)		40 (15)	
Treatment modality		< 0.001		< 0.001
OP alone (160, 24.0)	89 (17)		75 (39)	
OP + RT/CCRT (507, 76.0)	69 (147)		53 (235)	

DOI depth of invasion (defined as the measured thickness from the surface of the normal mucosa to the deepest portion of the tumor), *OP* operation, *RT* radiotherapy, *CCRT* concurrent chemoradiotherapy

[a]Unavailable data: pN status (no neck dissection, n = 15)

[b]Unknown data: margin status (n = 9)

TABLE 3 Multivariate analyses of 5-year disease-specific and overall survival rates in pT3-4 patients with buccal, gum, hard palate, and retromolar squamous cell carcinoma (n = 667)

Risk factor (n)[a]	Disease-specific survival		Overall survival	
	HR (95% CI)	p	HR (95% CI)	p
Tumor > 4 cm and DOI > 10 mm (n = 261)	1.477 (1.044–2.089)	0.027		ns
DOI > 20 mm (n = 157)	1.487 (1.033–2.140)	0.033	1.529 (1.191–1.963)	0.001
Through cortex/skin invasion (n = 362)		ns	1.301 (1.028–1.646)	0.029
Pathological N2-3b (n = 240)	3.995 (2.788–5.725)	< 0.001	2.501 (1.975–3.168)	< 0.001
Poor differentiation (n = 69)	1.736 (1.149–2.623)	0.009	1.499 (1.079–2.082)	0.016
Lymphatic invasion (n = 48)	1.599 (1.017–2.513)	0.042	1.491 (1.039–2.140)	0.030
Perineural invasion (n = 241)	1.451 (1.048–2.009)	0.025		ns

DOI depth of invasion, *HR* hazard ratio, *CI* confidence interval, *ns* not significant

[a]All of the factors identified in univariate analysis were entered into multivariate analyses. Only significant factors are presented in the table

study. Owing to the prospective collection of data on DOI and through cortex/skin invasion, we were able to reclassify all patients according to the new AJCC eight edition staging manual. We identified a tumor > 4 cm/DOI > 10 mm and DOI > 20 mm as independent RFs for 5-year DSS. We also identified DOI > 20 mm and through cortex/skin invasion as independent RFs for 5-year OS. Because the number of patients with a DOI > 20 mm was lower (n = 157) than that of those showing tumor > 4 cm/DOI > 10 mm (n = 261) and through cortex/skin invasion (n = 362), the adverse survival impact of DOI > 20 mm was clearly stronger than that of tumor > 4 cm/DOI > 10 mm and through cortex/skin invasion (Table 2; Fig. 2). This may be explained by the fact that patients with DOI > 20 mm more frequently had pN3b disease (33.3% vs. 29.0% and 27.7%), ENE (37.8% vs. 35.5% and 33.0%), and perineural invasion (43.9% vs. 42.5% and 39.5%) compared with those with tumor > 4 cm/DOI > 10 mm and cortex/skin invasion. These observations also may explain the higher use of adjuvant CCRT (45.2% vs. 39.1% and 37.6%) in the former group.

Notably, the optimal cutoff point for DOI in this study (> 20 mm vs. ≤ 20 mm) was identical to that suggested in the first revision of AJCC eight edition (2018) staging manual. Our analyses revealed that a DOI > 20 mm was a stronger prognosticator than the other two criteria used for identifying a tumor as pT4a. First, a DOI > 20 mm was an independent prognosticator for both DSS and OS rates, whereas a tumor > 4 cm/DOI > 10 mm showed an independent prognostic significance for DSS only. Similarly, through cortex/skin invasion independently predicted OS rates only (Table 3). We then examined the discriminatory capability of the three criteria used to identify pT4a disease. Although the visual discriminatory ability for 5-year DSS was appropriate for all of the three criteria, the lowest p value (3.8×10^{-18}) was observed for pT1/pT2/DOI ≤ 20 mm/DOI > 20 mm (Fig. 2a–c). As far as 5-year OS is concerned, the visual discriminatory ability of DOI > 20 mm and through cortex/skin invasion criteria was higher than that of tumor > 4 cm/DOI > 10 mm criterion. Notably, pT1/pT2/DOI ≤ 20 mm/DOI > 20 mm showed the highest discriminatory capacity as well (p value = 1.8×10^{-23}; Fig. 2d–f). Altogether, these data indicate that tumors with a DOI > 20 mm should be classified as T4a, notwithstanding that the second revision of the AJCC eight edition (2018) staging manual removed this criterion.

Although our report benefits from a large sample size, all of the patients had first primary OCSCC and were uniformly treated with surgery (either with or without adjuvant therapy). Therefore, the generalizability of our data needs to be confirmed in international multicenter studies.

All of the three criteria (tumor > 4 cm/DOI > 10 mm, DOI > 20 mm, and through cortex/skin invasion) identify high-risk patients, which should be reflected in further revisions of pT4a classification in OCSCC.

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