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The 8th TNM classification for oral squamous cell carcinoma: What is gained, what is lost, and what is missing☆

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ABSTRACT

Objectives: The 8th TNM edition remarkably changed the classification of T and N categories for oral squamous cell carcinoma (OSCC). The present study aims at evaluating the improvement in prognostic power compared to the 7th edition, pros and cons of the modifications, and parameters deserving consideration for further implementations.

Materials and methods: All OSCCs treated with upfront surgery at our institution between 2002 and 2017 were included. Demographics, clinical-pathological and treatment variables were retrieved. All tumors were classified according to both the 7th and 8th TNM edition, and patients were grouped according to the shift in T category and stage. Survivals were calculated with the Kaplan-Meier method. Univariate and multivariate analysis were carried out. Receiver Operating Characteristics (ROC) curve analyses were performed to find the best cut-off of DOI (in patients with DOI > 10 mm) and number of involved nodes (in positive neck patients).

Results: 244 patients were included. T, N categories, and stage changed in 59.2%, 20.5%, and 49.1% patients, respectively; 41.5% of patients were upstaged. The new T classification well depicted prognosis according to OS. Five-year overall (OS), disease-specific, recurrence-free (RFS) survivals were 60.5%, 70.9%, 59.8%, respectively. According to ROC curves, DOI > 20 mm and 4 positive nodes were the best cutoffs for OS and RFS.

Conclusion: The novelties introduced in 8th TNM edition were positive. DOI > 20 mm for T4 definition and number of positive nodes (0, < 4, 4 or more) for N classification emerged as the most urgent factors to be implemented.

Introduction

Oral cavity squamous cell carcinoma (OSCC) accounts for 8% of all malignancies and 30% of head and neck cancers [1]. Its incidence is steadily increasing worldwide and 5-year survival estimates remain unchanged despite significant improvements in diagnostic techniques and treatment strategies [1,2]. The tumor, node, and metastasis (TNM) staging system is the principal criterion to describe and stage tumor extension, as well as to guide, evaluate, and compare therapeutic strategies based on internationally-accepted guidelines [3,4]. The 8th Edition of the American Joint Committee on Cancer (AJCC) TNM staging system has been actively implemented since January 2018 [5]. Compared with the 7th Edition, OSCC staging criteria were relevantly modified. In particular, depth of invasion (DOI) and extranodal extension (ENE) were introduced as parameters to define the T and N category, respectively [6–10].

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The present study is aimed at evaluating the changes in classification, prognostic implications, and possible weaknesses of the novel TNM classification of OSCC based on a homogeneous cohort of patients treated over a 15-year period at a tertiary academic institution.

Materials and methods

Patient selection

All patients with OSCC treated at the Unit of Otorhinolaryngology – Head and Neck Surgery of the University of Brescia from January 2002 to August 2017 were included. All patients underwent upfront surgery including resection of the primary tumor and neck dissection. Exclusion criteria were: (1) distant metastasis at presentation; (2) previous and/or synchronous head and neck cancer; (3) follow-up unavailable; (4) history of cancer within the last 5 years (any site, any stage). During the study period, all pathological specimens were examined by dedicated head and neck pathologists; both DOI and ENE were consistently reported according to internationally accepted criteria. All OSCCs could be appropriately staged on the base of pathological reports according to both the 7th and 8th editions of the TNM classification. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice.

Treatment and follow-up

Each case was discussed in the multidisciplinary head and neck tumor board at our institution. Indications for treatment were given on a case-by-case basis according to the National Comprehensive Cancer Network (NCCN) guidelines available at the time of diagnosis. Adjuvant radiotherapy (RT) followed a standardized fractionation regimen (60–66 Gy on high-risk volume and 50–54 Gy on low-/intermediate-risk volume, in daily fractions of 1.8–2 Gy). Concomitant chemotherapy consisted of cisplatin either 100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly.

In the first 2 years after treatment, the follow-up schedule included clinical evaluation every 2 months and imaging assessment (computed tomography [CT] or magnetic resonance [MR] together with ultrasonography of the neck) every 4 months. Clinical and imaging examinations were subsequently performed every 6 months up to the 5th year and yearly thereafter [11,12]. CT of the thorax and abdomen, positron emission tomography (PET), or PET-CT were performed yearly during the first 5 years after treatment in patients deemed at high-risk of recurrence.

Statistical analysis

Statistical analysis was performed using a commercially available software (XLSTAT add-on for Microsoft Excel, version 2017.6.0; Addinsoft SARL, Paris, France). The following variables were included: age, gender, subsite of oral cavity (buccal mucosa, alveolar ridges, hard palate, tongue, floor of mouth) [13], tumor differentiation (well, moderate, or poor) [14], 7th and 8th TNM classification and stage, treatment, DOI, distance between excision margins and invasive front of the tumor, margin status, presence of bone, perineural, vascular invasion, ENE, count of involved and removed nodes, and nodal ratio (defined as the ratio between positive and removed nodes).

Descriptive statistics were performed obtaining distribution of categorical variables and mean, median, range, and interquartile range for continuous variables. A contingency table was obtained matching the 7th and 8th Edition-based T, N categories, and UICC/AJCC stage. According to the modifications of the T category observed comparing the 7th with the 8th edition, each case was included in one of the following groups:

- $T_{1/2\rightarrow1/2}$: tumors remaining T1 or T2 in both editions;
- $T_{4a\rightarrow1/2}$: tumors downstaged from T4a to T1 or T2;
- $T_{1/2\rightarrow3}$: tumors upstaged from T1 or T2 to T3;
- $T_{4a\rightarrow3}$: tumors downstaged from T4a to T3;
- $T_{4a\rightarrow4a}$: tumors remaining T4a in both Editions.

According to the modification of the assigned UICC/AJCC stage observed comparing the 7th to the 8th edition, each case was included in one of the following groups:

- I/II→I/II: tumors remaining stage I or II in both editions;
- II→III: tumors upstaged from stage II to stage III;
- III→III: tumors remaining stage III in both editions;
- IV→II: tumors downstaged from stage IV to stage II;
- IV→III: tumors downstaged from stages IVA/B to stage III;
- IV→IV: tumors remaining stage IVA or IVB in both editions;

Groups including less than 10 patients were excluded from statistical analysis. Associations between the modification of T, N categories, and DOI were assessed by Chi-square, Fisher's exact, Kruskal-Wallis, and/or Steel-Dwass-Critchlow-Fligner tests, as appropriate.

Overall (OS), disease-specific (DSS), recurrence-free (RFS), local recurrence-free (LRFS), regional recurrence-free (RRFS), and distant recurrence-free (DRFS) survivals were calculated with the Kaplan-Meier method. For each survival estimate, the entry time was the date of conclusion of treatments (surgery or adjuvant therapies). Survival analyses were made by univariate models based on log-rank test (categorical variables) or Cox proportional hazard model (continuous variables), as appropriate.

Variables with statistical significance at univariate analysis were considered eligible for the multivariate Cox proportional hazard model. In line with Harrell's guidelines [15], the maximum number of factors admitted in the multivariate model was calculated for each survival as 10% of observed events; if needed, a further selection of variables was made based on clinical relevance and redundancy of information. Only the 8th TNM edition was included in the prognostic model.

Finally, Receiver Operating Characteristics (ROC) curve analyses were performed considering death from any cause and recurrence of disease as events, and DOI (in patients with DOI $>$ 10 mm) and number of involved nodes (in positive neck patients) as the tests. Patients alive and free of disease with less than 6 months of follow-up were excluded from the analyses, respectively.

A Kaplan-Meier analysis with log-rank test of OS and RFS was performed using the cut-off values extrapolated from ROC curves. The level of significance was set at 0.05 for all statistical tests.

Results

Description of the series

The study included 244 patients. Complete demographic, clinical, and pathologic data are reported in Table 1. Male-to-female ratio was 1.7:1 with a median age of 64.1 years. The mobile tongue (50.4%) and floor of the mouth (20.9%) were the most frequently involved subsites. Lymph node metastases were diagnosed in 112 (45.7%) patients, with ENE reported in 56 (22.9%). Margins were clear in 139 (57.0%) patients, close in 66 (27.0%), and involved in 39 (16.0%). Adjuvant RT was offered to 146 patients (60.1%). Sixty patients (24.6%) also received concomitant platinum-based chemotherapy.

Mean follow-up was 32.8 months (range, 1.1–181.1). Tumor recurrence occurred in 86 (35%) patients: 52 (21.3%) local, 49 (20.1%) regional, and 32 (13.1%) at distant sites. Overall, 90 deaths were recorded, and 58 were cancer-related. Five-year estimates of OS, DSS, RFS, LRFS, RRFS, and DRFS were 60.5%, 70.9%, 59.8%, 74.3%, 74.5%, and 83.9%, respectively.

Table 1
Demographics and clinical-pathologic features of the series.

Demographics and clinical-pathologic variables		N (%)
Gender	Male	153 (62.7%)
	Female	91 (37.3%)
Mean age (years, range)		63.8 (26–98)
Subsite	Tongue	123 (50.4%)
	Floor of the mouth	51 (20.9%)
	Retromolar trigone	25 (10.2%)
	Alveolar ridge	26 (10.6%)
	Buccal mucosa	19 (7.8%)
Surgical Treatment		
Transoral resection		62 (25.1%)
Pull-through resection		182 (74.9%)
Neck dissection	Selective	133 (54.5%)
	Comprehensive	111 (45.7%)
	Unilateral	171 (70.4%)
	Bilateral	72 (29.6%)
Histopathological data		
Surgical margins	Negative	139 (57.0%)
	Close	66 (27.0%)
	Positive	39 (16.0%)
Grading	G1	85 (34.8%)
	G2	132 (54.1%)
	G3	25 (10.2%)
Mean depth of infiltration (range)		13.5 mm (0.5–92 mm)
Perineural invasion	Absent	116 (47.7%)
	Present	126 (52.3%)
Lymphovascular invasion	Absent	175 (72.0%)
	Present	68 (28.0%)
Mean number of removed nodes (range)		45.7 nodes (7–119)
Median number of nodal metastases (range)		1.6 nodes (0–20)
Mean lymph node ratio (range)		3.5% (0–20%)
Extranodal extension	Absent	186 (76.9%)
	Present	56 (21.1%)
Adjuvant treatments		
Adjuvant radiotherapy		146 (60.1%)
Concomitant chemotherapy		60 (24.6%)

TNM and stage modifications

Modifications of T, N categories, and stage are reported in Table 2. The analysis of pT category changes was feasible in 191 (78.3%) patients. Sixty-nine (36.1%) were reassigned to a lower pT category, mostly including cases of downstaging from pT4a to pT3. Conversely, 44 (23.1%) tumors were reassigned to a higher pT category, mostly due to a shifting from pT2 to pT3. In 40.8% of cases the pT category remained unchanged.

Analysis of pN category changes was feasible in all cases. In 50 (20.5%) patients, the nodal status was upstaged to pN3b due to ENE, which upstaged only 2 cases from pN1 to pN2a.

The analysis of stage modifications was definable for 205 (84.0%) cases. As a consequence of T and N shifting, stage migration was recorded in more than half of patients: 35 cases (17.1%) were downstaged, and 85 (41.5%) were upstaged. In particular, 20 (9.8%) patients shifted from an early (I-II) to an advanced stage (III-IV) due to an upstage in T category, and 56 (27.3%) patients shifted from stage IVA to stage IVB due to an upstage in N category (N3b). Overall, only 67 (35.1%) cases with all information available showed no change in terms of both T and N categories.

Table 2
Contingency table of the modifications of pathological T and N category and stage classification between 7th and 8th edition of TNM.

Total patients (N = 191)		pT classification (8th edition)			
		T1	T2	T3	T4
pT classification (7th edition)	T1	21	13	5	0
	T2	3	23	26	0
	T3	0	0	2	0
	T4	0	10	56	32

Total patients (N = 244)		pN classification (8th edition)						
		N0	N1	N2a	N2b	N2c	N3a	N3b
pN classification (7th edition)	N0	131	0	0	0	0	0	0
	N1	0	29	6	0	0	0	0
	N2a	0	0	2	0	0	0	1
	N2b	0	0	0	21	0	0	37
	N2c	0	0	0	0	4	0	12
	N3	0	0	0	0	0	0	0

Total patients (N = 206)		Stage classification (8th edition)				
		I	II	III	IVA	IVB
Stage classification (7th edition)	I	15	9	4	0	0
	II	2	18	15	1	0
	III	0	0	14	0	1
	IVA	0	3	30	38	55
	IVB	0	0	0	0	0

Impact of TNM and stage modifications on survival

Downstaged tumors $T_{4a\rightarrow1/2}$ and $T_{4a\rightarrow3}$ were associated with the highest rate of nodal metastasis ($p = 0.0004$), highest N category according to the 8th edition ($p = 0.006$), highest number of nodal involvement ($p = 0.0002$), and highest rate of ENE ($p = 0.001$) (Table 3). $T_{4a\rightarrow3}$ OSCCs had the highest DOI (median, 19.5 mm), which was significantly higher with respect to all other T-modification groups except for $T_{4a\rightarrow4a}$ tumors ($p < 0.0001$) (Table 4).

Fig. 1 and Supplementary Fig. 1 describes the impact of T reclassification on survival. OS drastically decreased when comparing patients with $T_{1/2\rightarrow1/2}$ tumors to all other patients. OS of patients with $T_{4a\rightarrow1/2}$ or $T_{4a\rightarrow4a}$ tumors continued to decrease at 5 years after treatment, whereas $T_{1/2\rightarrow3}$ or $T_{4a\rightarrow3}$ OSCCs showed a constant OS of around 50% in the long-term ($p = 0.0003$). DSS had a similar trend, except for the $T_{4a\rightarrow1/2}$ group, which showed a survival similar to $T_{1/2\rightarrow3}$ or $T_{4a\rightarrow3}$ cases ($p = 0.005$). When focusing on RFS, $T_{1/2\rightarrow3}$ group aligned with the $T_{1/2\rightarrow1/2}$ curve, while $T_{4a\rightarrow3}$ and $T_{4a\rightarrow1/2}$/$T_{4a\rightarrow4a}$ showed a stepwise decrease in survival rate ($p = 0.005$).

Fig. 2 and Supplementary Fig. 2 focuses on stage modifications and survival. OS was worst for patients with IV → IV and IV → II tumors, while the long-term prognosis was similar for patients with I/II → I/II, I/II → III, III → III, and IV → III ($p < 0.0001$). The DSS was 3-tiered according to the stage: I/II → I/II, IV → II, I/II → III, IV → III tumors showed the best survival, III → III showed an intermediate outcome, and IV → IV did worse ($p < 0.0001$). RFS was highest for I/II → I/II and I/II → III, intermediate for IV → III, and lowest for IV → II, III → III, and IV → IV tumors ($p < 0.0001$).

Prognosticators

The results of the univariate and multivariate analyses are summarized in Supplementary Tables 1 and 2. In multivariate analysis, T4a category was associated with decreased OS (OR = 12.78, CI 1.39–117.79; $p = 0.025$). DOI and perineural invasion were associated with decreased DSS (OR = 1.05, CI 1.01–1.10; $p = 0.019$) and DRFS (OR = 2.40, CI 1.10–5.23; $p = 0.028$), respectively.

Table 3
Summary of associations between T-reassignment and nodal disease load. ENE – Extranodal extension.

T modification	$T_{1/2\rightarrow1/2}$	$T_{4a\rightarrow1/2}$	$T_{1/2\rightarrow3}$	$T_{4a\rightarrow3}$	$T_{4a\rightarrow4a}$	p-Value
Patients with nodal metastasis (percentage)	16/70 (26.7%)	6/10 (60.0%)	12/30 (40.0%)	37/56 (66.1%)	11/31 (35.5%)	0.0004*
8th edition N category (percentages)	N0: 73.3%	N0: 40.0%	N0: 60.0%	N0: 33.9%	N0: 64.5%	0.006*
	N1: 10.0%	N1: 10.0%	N1: 10.0%	N1: 12.5%	N1: 6.5%	
	N2: 8.3%	N2: 0.0%	N2: 6.7%	N2: 17.9%	N2: 12.5%	
	N3: 8.3%	N3: 50.0%	N3: 23.3%	N3: 35.7%	N3: 16.1%	
Number of involved nodes (median; mean)	0.0; 1.0	1.5; 1.3	0; 1.2	2.0; 2.9	0; 1.1	0.0002**
Nodal metastasis with ENE (percentage)	10.0%	50.0%	23.3%	41.1%	19.4%	0.001***

* Chi-square.
** Kruskal-Wallis.
*** Fisher's exact test.

Table 4
Table summarizing the p-values of comparisons between T-modification groups in terms of depth of invasion (DOI), based on Kruskal-Wallis and Steel-Dwass-Critchlow-Fligner post-hoc tests.

T modification (median DOI)	$T_{1/2\rightarrow1/2}$ (6.0 mm)	$T_{4a\rightarrow1/2}$ (9.0 mm)	$T_{1/2\rightarrow3}$ (13.5 mm)	$T_{4a\rightarrow3}$ (19.5 mm)	$T_{4a\rightarrow4a}$ (17.0 mm)
$T_{1/2\rightarrow1/2}$ (6.0 mm)	1	0.015	< 0.0001	< 0.0001	< 0.0001
$T_{4a\rightarrow1/2}$ (9.0 mm)	0.015	1	0.002	< 0.0001	0.294
$T_{1/2\rightarrow3}$ (13.5 mm)	< 0.0001	0.002	1	0.004	0.860
$T_{4a\rightarrow3}$ (19.5 mm)	< 0.0001	< 0.0001	0.004	1	0.536
$T_{4a\rightarrow4a}$ (17.0 mm)	< 0.0001	0.294	0.860	0.536	1

The presence of nodal metastasis (pN1 to pN3 categories) was related to lower RFS (OR = 6.73, CI 2.62–17.25; p < 0.0001), LRFS (OR = 3.94, CI 1.45–10.71; p = 0.007), and RRFS (OR = 7.41, CI 2.63–20.89; p < 0.0001), while the pN3b category was associated with worse OS (OR = 3.80, CI 1.34–10.78; p = 0.012), DSS (OR = 5.42, CI 1.36–21.6; p = 0.017), and DRFS (OR = 4.57, CI 1.50–13.91; p = 0.008). The number of positive nodes was independently associated with a stepwise decrease of all outcomes. Adjuvant (chemo)RT was an independent protective factor in terms of OS (OR = 0.38, CI 0.00–0.85; p = 0.019) and RFS (OR = 0.43, CI 0.00–0.93; p = 0.032).

ROC curve analysis showed that among patients with DOI > 10 mm, DOI ≥ 22 mm was the cut-off value that provided the highest accuracy in terms of increased probability of death (area under the curve [AUC] = 0.563; p = 0.343) and recurrence (AUC = 0.622; p = 0.069). On the other hand, 4 or more pN + was the best prognostic cut-off value in positive necks (AUC = 0.636; p = 0.012 and AUC = 0.579; p = 0.156, respectively). OS and RFS worsened stepwise in OSCCs with DOI < 5 mm, ≥5 and < 10 mm, ≥10 and < 20 mm, and ≥ 20 mm (p = 0.0006 and p = 0.106, respectively; Fig. 3). The 20 mm cut-off was used instead of 22 mm to simplify a potential implementation into the T-classification. OS and RFS worsened stepwise in OSCCs with no nodal metastasis, less than 4 nodal metastases, and 4 or more involved nodes (p < 0.0001 and p < 0.0001, respectively; Fig. 3).

Discussion

In our study, the reallocation of patients according to the 8th edition of the TNM staging system demonstrated a remarkable impact on the distribution of T, N categories, and stage of OSCC, which changed in 59.2%, 20.5%, and 49.1% within the present series, respectively, compared to the 7th edition. These changes are of paramount importance when considering that T and N categories guide loco-regional treatment in patients without distant metastasis. The downstaging $T_{4a\rightarrow3}$ (36.1%) and the upstaging $T_{1/2\rightarrow3}$ (16.2%) were the most relevant modifications of T category as an effect of the exclusion of lingual extrinsic musculature invasion and inclusion of the DOI parameter for T assignment. Accordingly, pT3 experienced a remarkable shift from 3.3% to 46.6%. N category changed due to the presence of ENE, which caused a shifting to the pN3b category in 20.5% of patients, whereas in only 6 (2.5%) was the N-status uplifted from pN1 to pN2a. pN3 patients passed from being absent to being diagnosed in 22.1% of cases [16]. Overall, these changes produced downstaging and upstaging in 17.1% and 41.5% of OSCCs, respectively. More specifically, 20 patients (9.8%) would have been shifted from stage I-II "early disease" to stage III-IV "advanced disease", while only 3 (1.5%) would have been downstaged. All these modifications in T and N classification and staging are consistent with other published reports [17,18]. Such an important stage migration, and in particular the shift from early to advanced disease, convey relevant implications in treatment planning. Of note, a considerable number of patients would receive intensified therapeutic regimens according to the new TNM classification system. The soundness of this shift should be however validated in future, prospective series.

Although the population size of the present study is limited, the homogeneity of treatment and the direct source of information ensured the reliability of our data. The most relevant findings are hereby clustered in "gains", "losses", and "missing information" with the aim of providing an overview of the pros and cons of the current TNM edition for OSCC classification and presenting evidence for further improvements.

What is gained?

The new T classification system of OSCC may improve patient stratification according to OS. Specifically, tumors remaining T1/2 and T4a are associated with the best and worst outcomes, respectively, while several OSCCs previously defined as T1/2 or T4a and now assigned to T3 category share a homogeneous intermediate long-term OS trend (Fig. 1). Coherently, T4a tumors are associated with the poorest results when focusing on loco-regional control. These data are in accordance with literature, as several reports from all over the world demonstrated higher predictive accuracy of the 8th TNM edition [17–24].

Pathologic N3b category was an important negative prognosticator. In fact, patients with N3b tumors had dismal OS and DSS due to the increased rate of distant recurrence, independently of other prognostic factors. Interestingly, pN3b category was more predictive of poor prognosis than ENE alone. This suggests that a high number of positive nodes has a prognostic weight even in patients with ENE. In fact, patients with a single nodal metastasis with ENE were not significantly associated with poor prognosis. Of note, these patients are a minority, with most cases of ENE being observed in necks with multiple nodal metastases. As a side note, a criticism on pN3a allocation must be made in view of its rarity (it is absent in our series); a single pN3 category

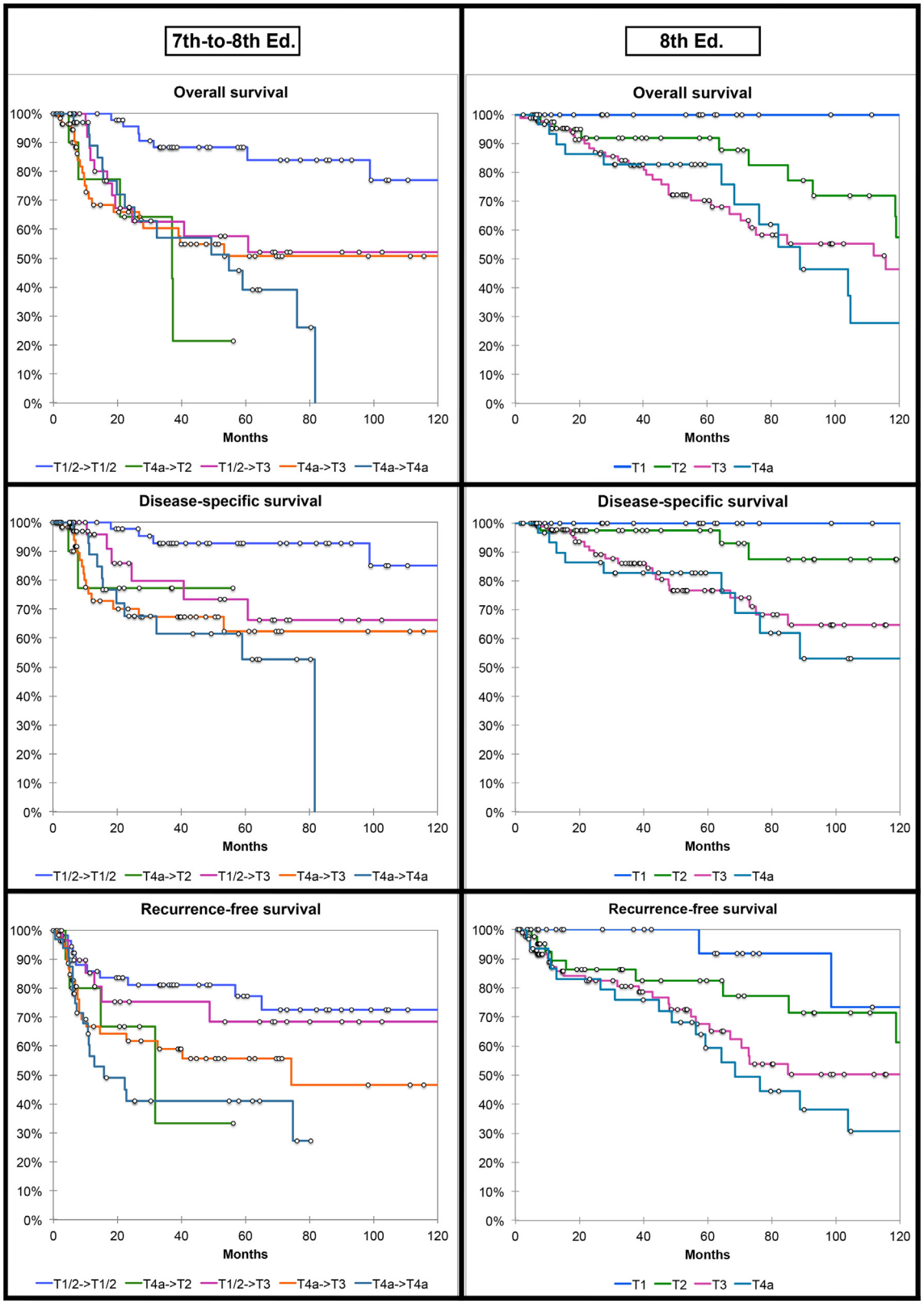

Fig. 1. Kaplan-Meier plots illustrating overall, disease-specific, and recurrence-free survival according to T category modification passing from the 7th to the 8th TNM edition (left column) and according to T category of the 8th TNM edition (right column).

would be simpler and still appropriate [25].

Perineural invasion was independently associated with worse DRFS. The 8th TNM edition systematically assesses this feature, thus ensuring a more consistent profiling of the disease and contributing, for the future, to possibly segregate lesions with this risk factor from those without.

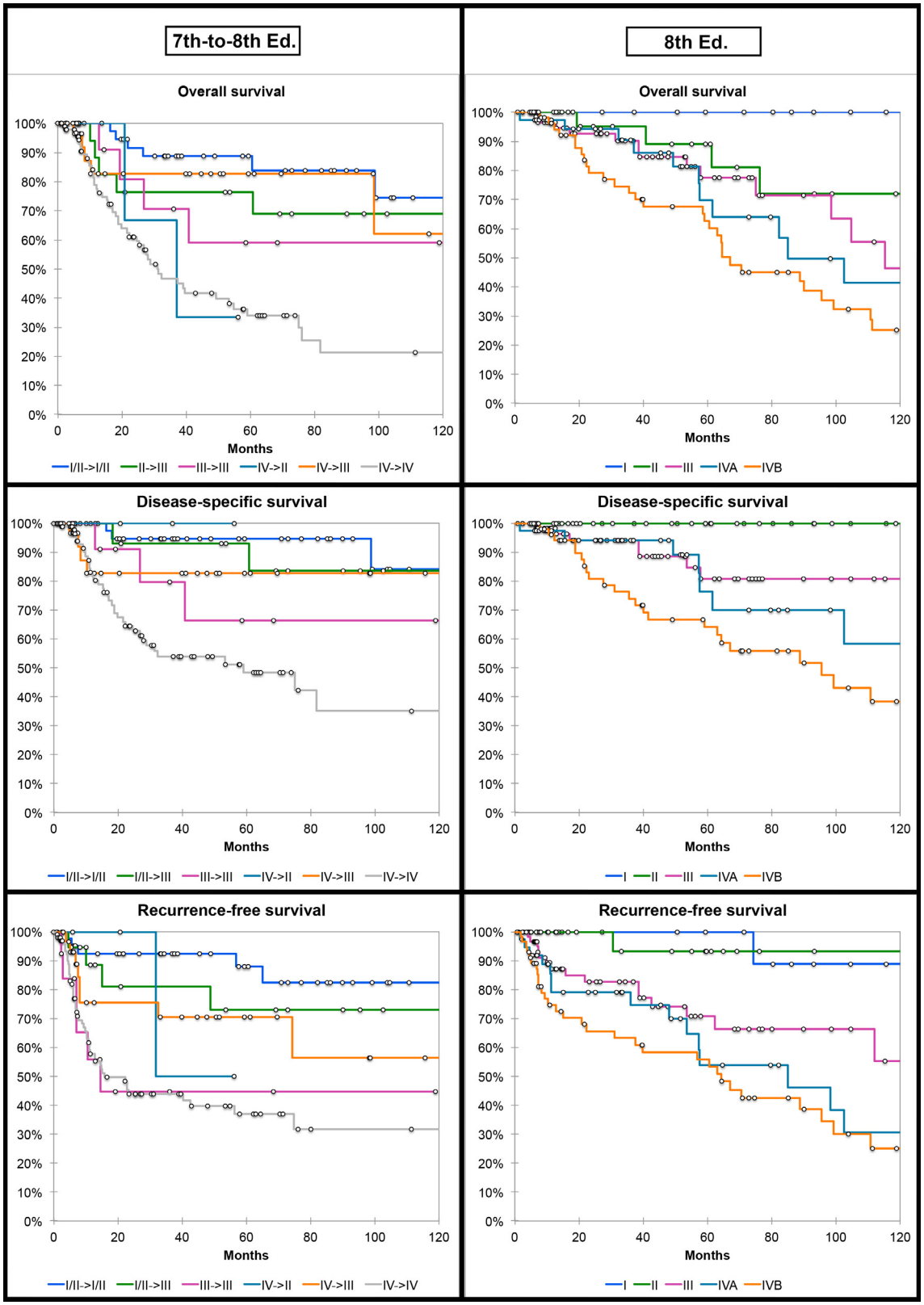

Fig. 2. Kaplan-Meier plots illustrating overall, disease-specific, and recurrence-free survival according to stage modification passing from the 7th to the 8th TNM edition (left column) and according to stage of the 8th TNM edition (right column).

What is lost?

When analyzing the probability and pattern of recurrence, T3 OSCCs according to the 8th edition showed a heterogeneous behavior, which conflicts with what previously mentioned with respect to OS. In fact, tumors defined as T4a according to the 7th edition were associated with a high propensity for recurrence regardless of reassignment to the T2, T3, or T4a category with the new system (Fig. 1). The pattern of

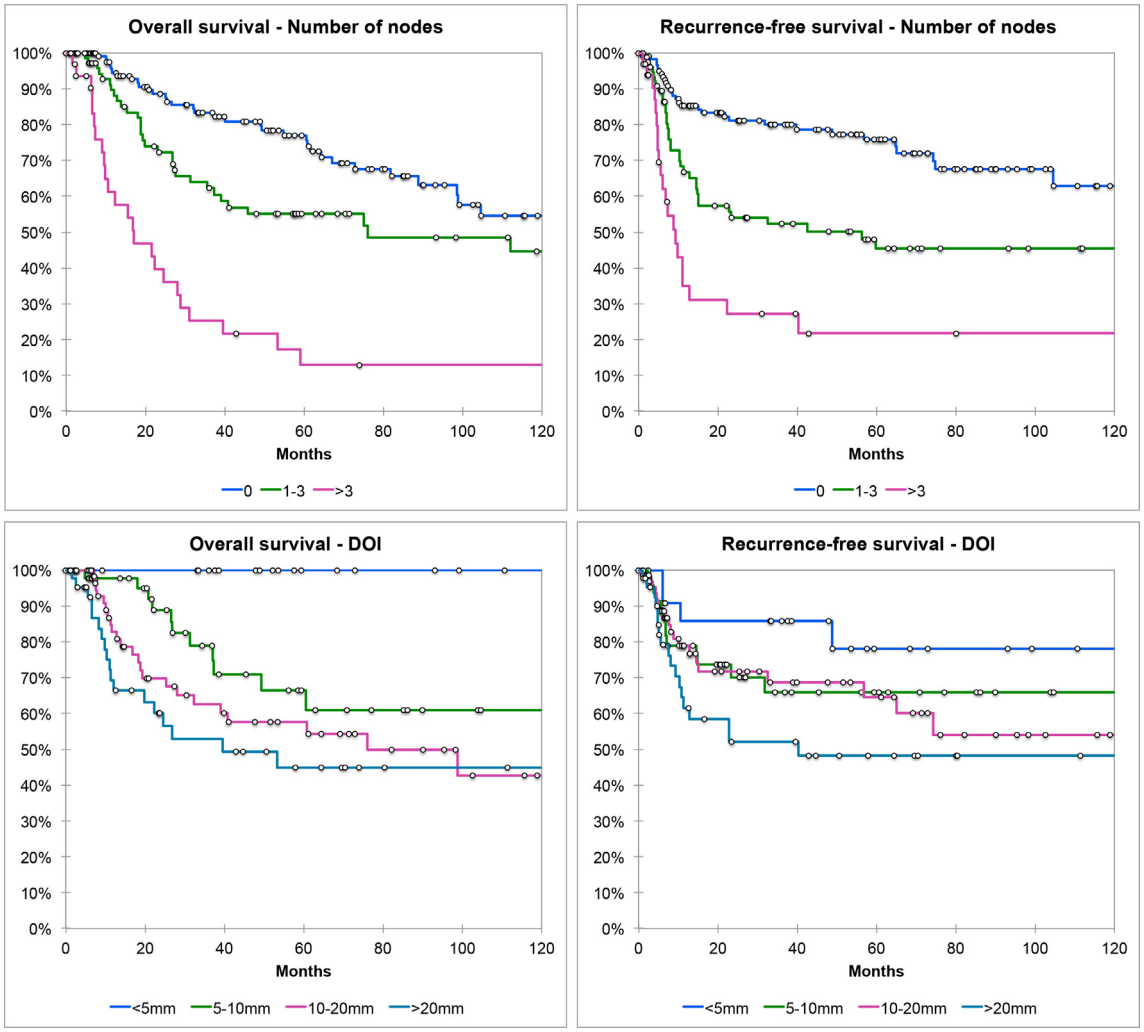

Fig. 3. Kaplan-Meier plots showing the stratification of overall and recurrence-free survival according to the number of involved nodes and depth of invasion (DOI).

recurrence varied from $T_{4a \rightarrow 3}$ tumors, showing preeminently regional and distant failure, to $T_{4a \rightarrow 4a}$ OSCCs, which typically recurred loco-regionally (Supplementary Fig. 1). Overall, these subsets of tumors, according to the criteria of T classification, correspond to OSCCs that extended to the extrinsic tongue muscles ($T_{4a \rightarrow 3}$ and $T_{4a \rightarrow 2}$) and/or the skin/bone framework surrounding the oral cavity ($T_{4a \rightarrow 4a}$). The poor prognosis shown by $T_{4a \rightarrow 3}$ OSCCs somehow conflicts with grouping these tumors together with $T_{1/2 \rightarrow 3}$ cases, which are those redefined as T3 due to DOI > 10 mm without invasion of bone and/or skin. The different behavior of these cancers is likely related to the disease load in the nodal basin, which is substantially higher for $T_{4a \rightarrow 3}$ and $T_{4a \rightarrow 2}$ OSCCs compared to other subsets (Table 3), and to the higher DOI observed in $T_{4a \rightarrow 3}$ tumors (median, 19.5 mm; Table 4). This concept reflects the debate on the role of extrinsic musculature invasion in defining T category. One can argue that definition of invasion of the extrinsic musculature of the tongue is mostly a clinical-radiological data and is difficult to assess on pathological examination. However, tumors previously labeled as T4a due to invasion of the extrinsic lingual muscles clearly have a different nodal status at presentation and a more ominous prognosis compared to those not having this pathological feature. As already demonstrated elsewhere [6], DOI is a potential surrogate of this feature, but possibly deserves a further stratification for subsites and for T4a classification.

What is missing?

The evidence that T3 according to the 8th Edition behave heterogeneously could be related to the absence of a DOI value determining the shift to the T4a category. According to the ROC and survival analysis, 20 mm could be a reasonable cut-off to further stratify OSCCs with DOI > 10 mm into T3 and T4a. This is supported by the evidence that OS continues to be independently affected by thickness of invasion even beyond 10 mm, and it is in line with the value proposed by Liao et al. [26,27]. From the anatomical point of view, it is worth remembering that a tongue tumor thickness > 20 mm potentially lead to subtotal if not total glossectomy.

The number of nodal metastases was independently associated with all survival outcomes, with 4 nodes resulting as the optimal cut-off to stratify patients. This finding perfectly aligns with that of Ho et al. [28], who reported that the number of nodal metastases serves as critical prognostic information that is capable of eclipsing other traditional prognosticators. The risk of death increased by 13% for each nodal metastasis according to the multivariate model. This was due to an increased risk for local, regional, and distant recurrence of 14%, 18%, and 13% for each involved node. These findings corroborate the acknowledged belief that the load of disease in the neck is a predominant prognosticator in OSCC, with the count of positive nodes being a much better predictor than laterality. Count of nodal metastases was demonstrated to be at least as reliable and repeatable as lymph nodal ratio, which in turn is considerably affected by the extent of neck

dissection and processing protocol of the surgical specimen [29]. Moreover, the number of involved nodes was found to reliably predict the benefit from concomitant chemotherapy in the adjuvant setting [30].

Currently, perineural spread is systematically assessed but does not bring the tumor to a higher stage. However, the risk of distant relapse during follow-up was more than doubled in case of perineural growth, regardless of other factors. In previous studies, perineural invasion improved the accuracy of prognostication when combined with other clinical-pathological factors (tumor grade, thickness, volume, nodal status, bone infiltration, neutrophils-to-lymphocytes ratio) [31–34]. This supports the possibility to emphasize the weight of perineural spread in the decision-making for adjuvant treatments. However, dedicated studies are mandatory before reaching firm conclusions on this topic.

T classification and natural history of OSCC

Finally, the results of the present study can help in depicting the natural history of OSCC. In the early phases ($T_{1/2\rightarrow1/2}$), OSCC grows superficially, leading to a 26.7% rate of nodal involvement, mostly consisting of single metastasis [35]. Patients usually have a favorable prognosis even with single-modality treatment. Subsequently, the tumor deepens into the surrounding tissues ($T_{1/2\rightarrow3}$), nearly doubling the frequency and load of neck disease. The 8th TNM Edition reliably highlights this aspect by upstaging cases previously defined as T1/2 [36,37]. At the last stage of its natural history, OSCC reaches deeply located soft tissues and/or bony structures ($T_{4a\rightarrow2}$, $T_{4a\rightarrow3}$, and $T_{4a\rightarrow4a}$). In tumors invading the deep soft tissues (i.e. those previously defined T4a due to invasion of the extrinsic tongue musculature), the rate of nodal involvement is as high as 60.0–66.1%, with ENE being detected in 41.1–50.0% of positive necks. These tumors have the highest propensity for regional and distant recurrence, thereby deserving a proportionally aggressive treatment that frequently consists of surgery with adjuvant (chemo)RT. In our opinion, downstaging the T category in these tumors might not adequately reflect their advanced phase of growth and consequent treatment requirements. As already mentioned, this aspect could be corrected by introducing a DOI cut-off for T4a tumors of > 20 mm. OSCCs extended to the maxillofacial skeleton or skin (i.e. invariably classified as T4a) do not show a considerable increase in terms of neck involvement with respect to $T_{1/2\rightarrow3}$ tumors. Nevertheless, these cancers are more prone to recur locoregionally during follow-up. Further studies are needed to depict the biological characteristics of tumors in these different stages, in order to gain information about the molecular derangements leading to tumor growth and provide new insights for a more tailored clinical approach.

Conclusion

With the limitations ensuing from the retrospective nature and restricted sample size of this study, our findings suggest that the introduction of the last TNM edition has provided some steps forward in delineating tumor characteristics and outcomes. Future revisions should address the needs which are emerging for further refinements. Based on our data, DOI > 20 mm for T4 definition and number of positive nodes for N classification are the most urgent factors to be implemented.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2020.104937.

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