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Original Research

Integrating depth of invasion in T classification improves the prognostic performance of the American Joint Committee on Cancer primary tumor staging system for cutaneous squamous cell carcinoma of the head and neck

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Abstract ***Background:*** The last revision of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual included a specific system for cutaneous squamous cell carcinoma (CSCC) of the head and neck. Here, we assessed the prognostic performance of six candidate modified T-classification models in head and neck CSCC patients.

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carcinoma;
AJCC;
Prognosis;
Survival

Methods: Analysis of 916 patients with head and neck CSCC given treatment with curative intent at The University of Texas MD Anderson Cancer Center between 1995 and 2019 was performed. The main outcome was disease-specific survival (DSS), and the impact of depth of invasion (DOI) was analyzed using multivariable regression models. Candidate models were developed using the optimal DOI cut points for each AJCC T classification based on goodness of fit of the model and the simplicity of the model. Staging systems were compared using Harrell's concordance index.

Results: Median age was 70 years (range, 19–97years) and median follow-up time of 22 months (range, 1–250months). The median DOI was 6.0 mm (range, 0.1–70.0 mm). The five-year DSS rate was 80.7% (95%CI, 77.4–83.7%). We found significant association between DOI (hazard ratio, 1.21 [95%CI: 1.01–1.43]) and DSS on multivariable analysis. Based on a low Akaike information criterion score, improvement in the concordance index, and Kaplan–Meier curves, model 6 surpassed the AJCC staging system.

Conclusions: Incorporation of DOI in the current AJCC staging system improves discrimination of T classifications in head and neck CSCC patients.

Lay summary: The current staging system for head and neck cutaneous squamous cell carcinoma demonstrates wide prognostic variability and provides suboptimal risk stratification. Incorporation of depth of invasion in the T-classification system improves risk prediction and patient counseling.

Precis: We propose improved head and neck cutaneous squamous cell carcinoma T staging that will include depth of invasion and should be considered in future versions of the American Joint Committee on Cancer after external validation.

1. Introduction

The eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual introduced the incorporation of pathological features into major T classification for head and neck squamous cell carcinoma (HNSCC) [1]. Recognizing the prognostic power of newly validated pathologic features, in addition to incorporating the head- and neck-specific cutaneous malignancies chapter, head and neck chapters of the AJCC Cancer Staging Manual, eighth edition, introduce significant changes from the seventh edition of some primary tumors. The most significant update creates a separate staging algorithm for high-risk human papillomavirus-associated oropharyngeal cancer (OPC) distinguishing it from OPC caused by other causes [1].

The AJCC made these changes in response to increasing recognition that the prognostic performance of the seventh edition of the manual was suboptimal for patients with cutaneous squamous cell carcinoma (CSCC) of the head and neck [2,3]. Notable additions to the eighth edition were the incorporation of extranodal extension (ENE) for human papillomavirus–negative HNSCC cases and depth of invasion (DOI) in oral cancer. Incorporation of these factors into clinical practice can produce more tailored application of adjuvant therapies and improved outcomes in HNSCC patients. For this reason, the College of American Pathologists recognized the need for standardization of specialized head and neck pathology synoptic reports [4,5]. This led to routine reporting of a defined set of pathological features, including DOI [6–8].

DOI is included in the AJCC classification of cancers besides HNSCC, such as cutaneous melanoma and uterine cervical cancer [9]. For CSCC, DOI is used only for T3 cancers, defined as those invading the subcutaneous fat deeper than 6 mm. More detailed delineation and incorporation of DOI for risk stratification for both early- and late-stage CSCC could prove beneficial. The present study aimed to conceive a new staging system with improved prognostic performance for CSCC that utilizes DOI. We compared the prognostic performance of multiple staging models including the current AJCC and previously reported pathology-based staging systems.

2. Materials and methods

2.1. Patients

This study was approved by The University of Texas MD Anderson Cancer Center Institutional Review Board and included patients treated between May 1995 and September 2019. Patients with histologically confirmed CSCC undergoing curative-intent surgery were candidates for this study (N = 1360). Patients were excluded if they had less than 1 month of follow-up or inadequate pathological information, including DOI. Of

the 1360 candidates considered for inclusion, 444 were excluded because of missing information. The final cohort consisted of 916 patients. Their tumors were classified in a uniform manner using the eighth edition of the AJCC Staging Manual [1]. Demographic, clinical, and pathological data were extracted from the patients' electronic medical records and stored in a REDCap database [10].

Table 1
Clinicopathological characteristics of the study patients with head and neck CSCC (N = 916).

Characteristic	N	%
Mean (±standard deviation) age, years	69.7 ± 11.4	
Sex		
Male	799	87.2
Female	117	12.8
Immunosuppression		
No	696	76.0
Yes	220	24.0
pT classification		
T1	447	48.8
T2	127	13.9
T3	276	30.1
T4	66	7.2
Pathological nodal classification		
N0	813	88.8
N1	30	3.3
N2a	0	0
N2b	19	2.1
N2c	0	0
N3	54	5.9
TNM stage[a]		
I	420	45.9
II	109	11.9
III	254	27.7
IV	133	14.5
ENE (N = 106)		
No	52	49.1
Yes	54	50.9
Surgical margin		
Negative	709	77.4
Close (<5 mm)	57	6.2
Positive	150	16.4
Adjuvant therapy		
None	602	65.7
Radiotherapy	240	26.2
Radiotherapy and systemic therapy	74	8.1
Decade of primary tumor treatment		
1995–2004	149	16.3
2005–2014	389	42.5
2015–2019	378	41.3

AJCC, American Joint Committee on Cancer; ENE, extranodal extension; TNM, tumour-node-metastasis.
[a] Eighth edition of the AJCC Cancer Staging Manual.

2.2. Histopathological analysis

Tissue processing and analysis were done in accordance with institutional guidelines, with assessments of DOI performed by head and neck pathologists and dermatopathologists. DOI was defined as the extent of tumor invasion beyond the basement membrane to the deepest point of tumor invasion and quantified in millimeters [1].

Table 2
Summary data for primary head and neck CSCC DOI in the study patients (N = 916).

Variable	N	%	DOI (mm)	
			Mean (SEM)	*P*
Sex				
Male	799	87.2	9 (0.3)	0.0330
Female	117	12.8	7 (0.8)	
Immunosuppression				
No	696	76.0	9 (0.3)	0.5650
Yes	220	24.0	7 (0.6)	
pT classification				
T1	447	48.8	4 (0.3)	<0.0010
T2	127	13.9	11 (0.6)	
T3	276	30.1	14 (0.4)	
T4	66	7.2	16 (0.9)	
Pathological nodal classification				
N0	813	88.8	8 (0.3)	<0.0001
N1	30	3.3	15 (1.6)	
N2a	0	0	NA	
N2b	19	2.1	14 (2.0)	
N2c	0	0	NA	
N3	54	5.9	15 (1.2)	
TNM stage				
I	420	45.9	4 (0.3)	<0.0001
II	109	11.9	11 (0.7)	
III	254	27.7	13 (0.4)	
IV	133	14.5	16 (0.6)	
ENE				
No	862	94.1	8 (0.3)	<0.0001
Yes	54	5.9	15 (1.2)	
Surgical margin				
Negative	709	77.4	9 (0.3)	0.0080
Close (<5 mm)	57	6.2	10 (1.1)	
Positive	150	16.4	7 (0.7)	
Adjuvant therapy				
None	602	65.7	6 (0.3)	<0.0001
Radiotherapy	240	26.2	14 (0.5)	
Radiotherapy and systemic therapy	74	8.1	14 (0.9)	
Decade of primary tumor treatment				
1995–2003	149	16.3	11 (0.8)	<0.0001
2004–2012	389	42.5	10 (0.6)	
2013–2019	378	41.3	8 (0.3)	

CSCC, cutaneous squamous cell carcinoma; DOI, depth of invasion; ENE, extranodal extension; NA, not available; SEM, standard error of the mean; TNM, tumour-node-metastasis.

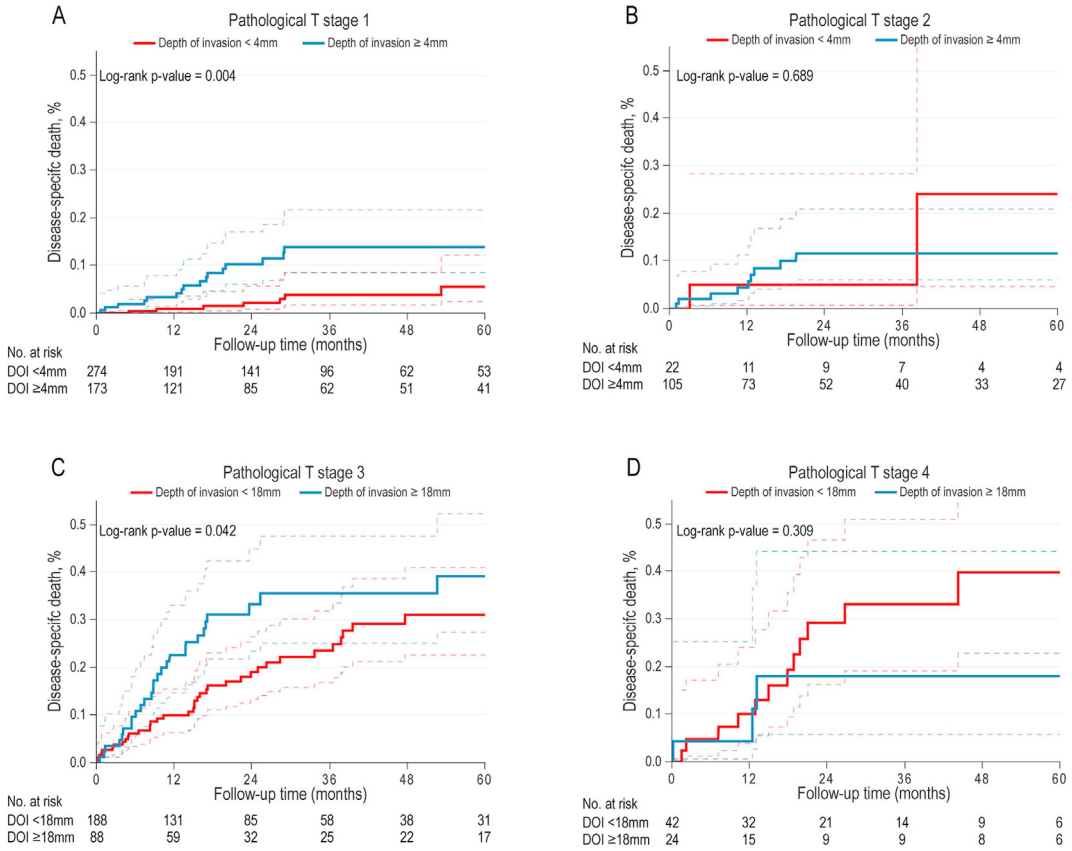

Fig. 1. Kaplan–Meier cumulative risk plots with risk tables demonstrating the association between DOI and disease-specific death for each pT classification in the study patients with head and neck CSCC staged using the eighth edition of the AJCC Cancer Staging Manual. (A) T1. (B) T2. (C) T3. (D) T4. A log-rank test was used for each comparison. AJCC, American Joint Committee on Cancer; CSCC, cutaneous squamous cell carcinoma; DOI, depth of invasion; pT, pathological tumor.

2.3. Model development

The prognostic significance of DOI beyond pathological tumor (pT) and pathological nodal classification was analyzed with DOI used as a continuous variable in a multivariable Cox regression model minimally adjusted for age, the overall tumor stage (I, II, III, or IV), adjuvant therapy, and the time period of primary tumor treatment (1995–2003, 2004–2012, or 2013–2019). The fully adjusted model was then used to assess the potential impact of sex, ENE, and margin status on the proposed models performance.

To develop a parsimonious regression model we identified the cut points used to dichotomize DOI. We used the Akaike information criterion (AIC) [11] and then compared with the baseline model using a likelihood ratio test to determine the goodness of fit of the model and the simplicity of the model. Optimal cut points were validated using a time-sensitive receiver operating characteristic curve in regression models using disease-specific survival (DSS) as an outcome.

Six candidate pT-classification models were compared using Harrell's concordance index (C-index) [12]. Risk stratification was confirmed by visual inspection of Kaplan–Meier curves. The proposed models were compared with the current AJCC staging system and previously proposed modifications of T classification based on DOI by Breuninger *et al.* [2] To calculate C-indices, Stata/IC software (version 14.2; StataCorp, College Station, Texas) was used.

2.4. Statistical analysis

All statistical tests were two-sided, and *P* values less than 0.05 were considered significant. Categorical data were analyzed using a chi-square test, normally distributed continuous data were analyzed using one-way analysis of variance, and skewed continuous data were analyzed using the Kruskal–Wallis test. All statistical testing was completed using SAS JMP Pro software (version 14.0.0; SAS Institute Inc., Cary, North Carolina). The primary clinical end-point of interest was DSS calculated from the time of primary surgical treatment to death resulting from CSCC. Overall survival was calculated from the date of surgery to the date of death or the last follow-up visit.

Table 3
Multivariable analysis of clinicopathological factors associated with DSS in the study patients with head and neck CSCC.

Factor	Minimally adjusted model		Fully adjusted model	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary tumor DOI	1.21 (1.01–1.45)	0.038	1.20 (1.01–1.44)	0.040
Age	1.02 (1.01–1.04)	0.001	1.02 (1.01–1.04)	<0.001
Decade of primary tumor treatment		0.767		
1995–2003	Referent		Referent	0.687
2004–2012	0.93 (0.54–1.62)	0.808	0.80 (0.52–1.58)	0.722
2013–2019	1.09 (0.67–1.83)	0.711	1.10 (0.67–1.85)	0.702
Sex				0.606
Male	–		Referent	
Female	–		0.85 (0.43–1.51)	0.606
Pathological stage[a]		<0.001		<0.001
I	Referent		Referent	
II	1.69 (0.67–3.96)	0.248	1.66 (0.66–3.88)	0.265
III	4.67 (2.53–8.96)	<0.001	4.65 (2.52–8.92)	<0.001
IV	6.62 (3.41–13.23)	<0.001	6.34 (3.10–13.17)	<0.001
ENE				0.644
No	–		Referent	
Yes	–		1.16 (0.61–2.17)	0.644
Surgical margin				0.737
Negative	–		Referent	
Close (<5 mm)	–		1.03 (0.48–1.95)	0.912
Positive	–		1.23 (0.73–2.20)	0.440
Adjuvant therapy		0.346		0.329
None	Referent		Referent	
RT	0.99 (0.63–1.56)	0.971	0.98 (0.62–1.55)	0.937
CRT	1.46 (0.79–2.62)	0.211	1.45 (0.79–2.61)	0.224

Abbreviations: AJCC, American Joint Committee on Cancer; CIs, confidence intervals; CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy..
[a] Eighth edition of the AJCC Cancer Staging Manual.

3. Results

3.1. Patient demographics

The patients were 799 (87%) men, with a median age of 70 years (range, 19–97 years) and median follow-up time of 22 months (range, 1–250 months), Table 1. We noted variation in the distribution of these characteristics among time periods (1995–2003, 2004–2012, or 2013–2019), with differences in mean age ($P = .003$), pT classification ($P < .001$), pathological nodal classification ($P < .001$), DOI ($P = .020$), ENE ($P < .001$), margin status ($P = .003$), and adjuvant therapy use ($P < .001$).

3.2. Primary tumor DOI

The mean (±SEM) DOI was 8.9 mm ± 0.3 mm. Increasing DOI was associated with earlier time period of primary tumor treatment (i.e. 1995–2003), male sex; advanced disease (stage III–IV), including high pT and pathological nodal classifications; the use and type of adjuvant therapy, and close margins, Table 2. Median DOIs and DOI ranges varied based on pT classification: 3.0 mm (0.1–20.0 mm) for pT1, 10.0 mm (0.5–40.0 mm) for pT2, 11.0 mm (0.4–70.0 mm) for pT3, and 14.0 mm (2.0–42.0 mm) for pT4 cancers.

3.3. Model performance assessment

The five-year DSS rate was 80.7% (95% confidence interval [CI], 77.4–83.7%), with 120 deaths due to CSCC, Fig. 1. After adjustment for age, overall stage, adjuvant therapy, and time period of treatment DOI was still associated with DSS (hazard ratio, 1.21 [95% CI: 1.01–1.43]), Table 3. Using the fully adjusted model, we confirmed that the results were robust after additional adjustment for sex, margin status and ENE. We found significant improvement in model fit for DSS with and without DOI and with inclusion of the overall stage ($P < .001$), Taken together, these data indicate that DOI and overall stage provide non-overlapping prognostic information.

Next, we used regression model's AIC values, to dichotomize the DOI; the DOI cut points were less than 4 mm versus at least 4 mm for pT1 and pT2 and less than 18 mm versus at least 18 mm for pT3 and pT4. The inclusion of T-classification–specific cut points for dichotomizing DOI significantly improved the model fit of the current AJCC staging system for pT1 ($P = .004$)

Table 4
T Classifications for Primary Head and neck CSCC in the Eighth Edition of the AJCC Cancer Staging Manual, Our Six Candidate Models, and a Previously Reported Staging System.

T classification	Description
AJCC[a]	
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension, minor bone erosion, perineural invasion, or deep invasion (defined as invasion beyond the subcutaneous fat or >6 mm as measured from the granular layer of adjacent normal epidermis to the base of the tumor)
T4	Tumor with gross cortical bone/marrow and skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
Model 1	
T1	Maximum depth of invasion <4 mm
T2	Maximum depth of invasion ≥4 mm but <18 mm
T3	Maximum depth of invasion ≥18 mm
T4	AJCC T4, any depth of invasion
Model 2	
T1	AJCC T1-2, maximum depth of invasion <4 mm
T2	AJCC T1, maximum depth of invasion ≥4 mm; or AJCC T2, maximum depth of invasion ≥4 mm but <18 mm
T3	AJCC T2, maximum depth of invasion ≥10 mm; or AJCC T3-4, maximum depth of invasion <18 mm
T4	AJCC T3-4, maximum depth of invasion ≥18 mm
Model 3	
T1a	AJCC T1, maximum depth of invasion <4 mm
T1b	AJCC T1, maximum depth of invasion ≥4 mm
T2	AJCC T2, maximum depth of invasion <18 mm
T3	AJCC T2, maximum depth of invasion ≥18 mm; or AJCC T3-4, maximum depth of invasion <10 mm
T4	AJCC T3-4, maximum depth of invasion ≥18 mm
Model 4	
T1	AJCC T1, maximum depth of invasion <4 mm
T2	AJCC T1, maximum depth of invasion ≥4 mm; AJCC T2, maximum depth of invasion <18 mm
T3	AJCC T2, maximum depth of invasion ≥18 mm; or AJCC T3-4, maximum depth of invasion <18 mm
T4	AJCC T3-4, maximum depth of invasion ≥18 mm
Model 5	
T1a	AJCC T1, maximum depth of invasion <4 mm
T1b	AJCC T1, maximum depth of invasion ≥4 mm
T2	AJCC T2, maximum depth of invasion <18 mm
T3	AJCC T2, maximum depth of invasion ≥18 mm; or AJCC T3, maximum depth of invasion <18 mm
T4	AJCC T3, maximum depth of invasion ≥18 mm; or AJCC T4
Model 6	
T1	AJCC T1, maximum depth of invasion <4 mm
T2	AJCC T1, maximum depth of invasion ≥4 mm; or AJCC T2, maximum depth of invasion <18 mm
T3	AJCC T2, maximum depth of invasion ≥18 mm; or AJCC T3, maximum depth of invasion <18 mm
T4	AJCC T3, maximum depth of invasion ≥18 mm; or AJCC T4
Staging system based on pT stage [2]	
No risk	Tumor thickness ≤2 mm
Low risk	Tumor thickness >2 mm but ≤6 mm
High risk	Tumor thickness >6 mm

AJCC, American Joint Committee on Cancer; pT, pathological tumor.
[a] Eighth edition of the AJCC Cancer Staging Manual.

and pT3 ($P = .042$) but not for pT2 ($P = .689$) or pT4 ($P = .309$).

We developed six candidate T-classification models for assessment, Table 4. In model 1 we used DOI alone; this model performed worse compared with the other models (Figs. 1 and 2B), indicating that DOI provides additional, rather than overlapping, prognostic value to the AJCC classification. In addition, model 2 (i.e. classifying all tumors smaller than 4 cm as T1 if their DOI was less than 4 mm) did not differentiate T1 from T2 classifications (Fig. 2C, see Supporting Fig. S1 for patient distribution in each model). We designed models 3 and 5 to address this issue in early-stage tumors. Still, the 95% CIs for early T categories overlapped considerably in models 3 and 5 (Fig. 2D and F). Models 4 and 6 (Fig. 2) were optimal based on a combination of the AIC, Bayesian information criterion, and C-index, resulting in stratification of patients with early-stage disease into distinct risk groups.

The current AJCC staging system failed to discriminate T3 and T4 tumors (Fig. 2A). Model 6 had a lower AIC score, with better risk stratification for both early and advanced disease, and significant increase in the C-index, compared with the AJCC staging system. We then compared model 6 with the Breuninger *et al.* staging system [2]. Model 6 was more informative based on a better C-index, lower AIC score, and superior stratification of patients into risk groups. Model 6 also had better area under the receiver operating characteristic curve, with the difference statistically significant for the stages in the system described by Breuninger et al. [2] ($P = .010$). Moreover, model 6 outperformed the other models when overall survival was used as the end-point (Fig. 3).

Supporting Fig. S2 summarizes the similarities and differences in the T classification of CSCC in the study patients when comparing the AJCC system and model 6 in our proposed system. The T classification was the same in 68.2% of the patients and upstaged using model 6 in 31.8%. Specifically, T1 tumors in 38.7% of the patients migrated to T2 tumors with a DOI of at least 4 mm, T2 tumors in 23.6% of the patients migrated to T3 tumors with a DOI of at least 18 mm, and T3 tumors in 31.8% of the patients migrated to T4 tumors with a DOI of at least 18 mm.

4. Discussion

In its latest update, the AJCC introduced major modifications to staging of primary non–human papillomavirus HNSCC. Suboptimal prognostic performance of T classification for mucosal HNSCC in many patients resulted in the adoption of a staging incorporating tumor size and DOI in the oral cavity [13,14]. In addition, researchers identified head and

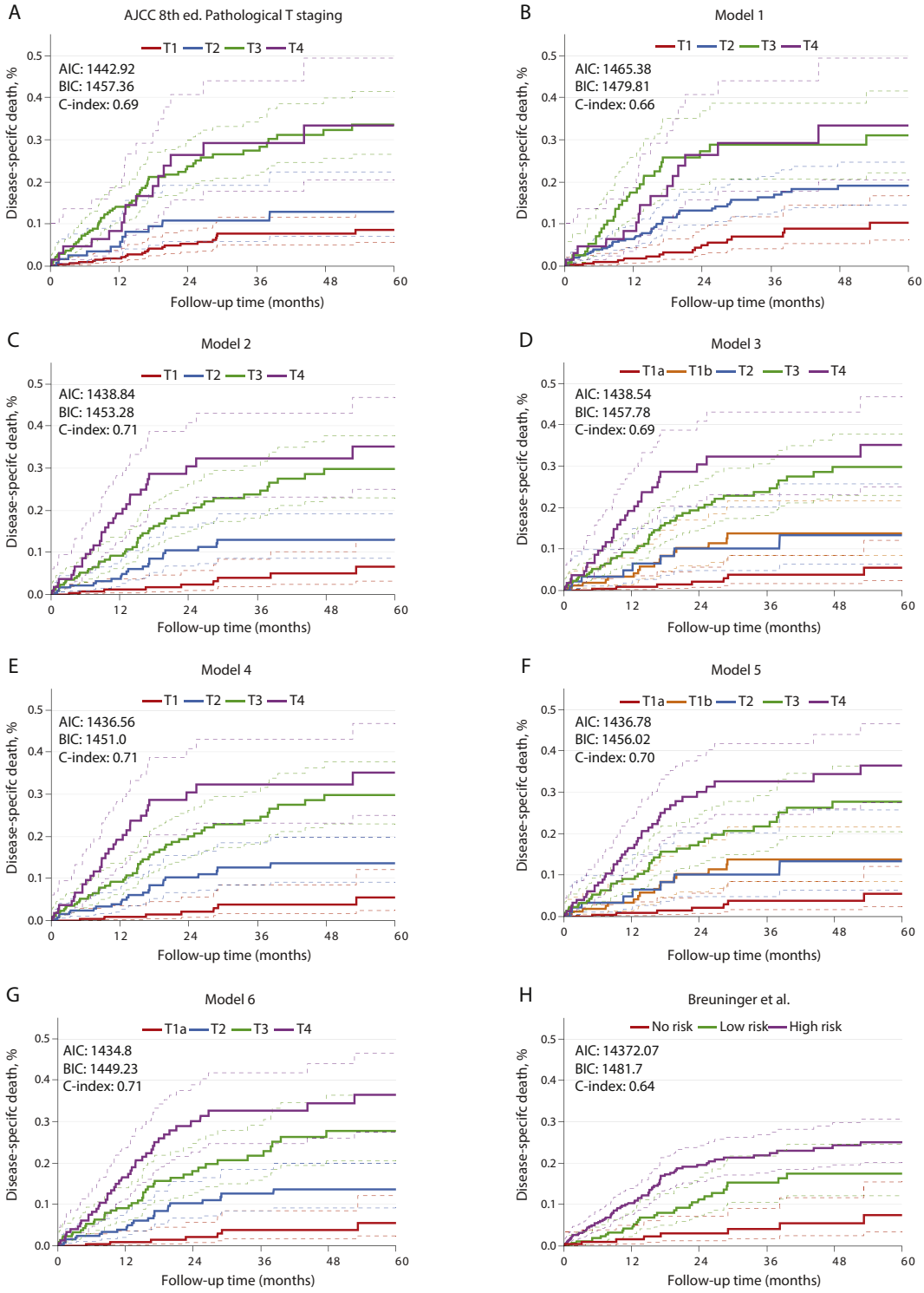

Fig. 2. Kaplan–Meier cumulative risk plots with 95% CIs demonstrating the ability of different staging systems to describe the primary tumor T classifications and disease-specific deaths in the study patients with head and neck CSCC. (A) Current AJCC T staging. (B–G) Models 1 (B), 2 (C), 3 (D), 4 (E), 5 (F), and 6 (G) in our proposed system. (H) The staging system proposed by Breuninger *et al.* [2] The dashed lines indicate 95% CIs. AJCC, American Joint Committee on Cancer; CIs, confidence intervals; CSCC, cutaneous squamous cell carcinoma; AIC, Akaike information criterion; BIC, Bayesian information criterion.

neck CSCC as an independent risk category; therefore, the AJCC developed a staging system specifically for it. In the present study, we looked at primary tumor classification based mainly on anatomical features recommended by the AJCC and assessed alternative clinicopathological features as independent prognostic factors in patients with CSCC of the head and neck. We found that the

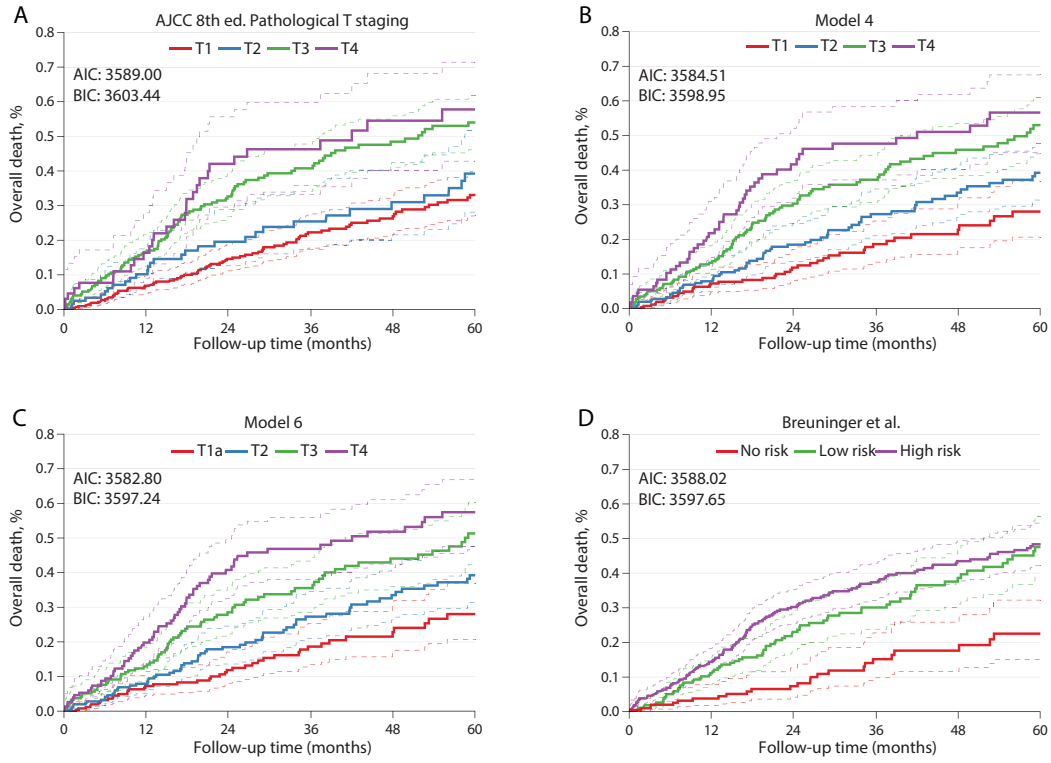

Fig. 3. Kaplan–Meier cumulative risk plots with 95% CIs demonstrating the association between overall death rate and T classification as per different staging systems. (A) The current AJCC staging system. (B) Model 4 in our proposed staging system. (C) Model 6 in our proposed staging system. (D) The staging system proposed by Breuninger *et al.* [2] The dashed lines indicate 95% CIs. AJCC, American Joint Committee on Cancer; CIs, confidence intervals; AIC, Akaike information criterion; BIC, Bayesian information criterion.

incorporation of DOI in the current AJCC staging system offers better risk stratification among T classifications for both DSS and overall survival.

We generated a staging system with six models that are modifications of the existing AJCC T classifications. One model (model 6) emerged with superior prognostic and stratifying capacity when compared with the current AJCC staging system and a system proposed by Breuninger *et al.*, [2] with excellent stratification of tumors into definite risk groups and relative simplicity (Table 4).

Despite the relatively long period of the study, we routinely reported DOI in pathology synoptic reports in our institution throughout the study duration. If this pathological metric is to be introduced into the AJCC staging system, providing a clear DOI definition is important as difference in pathology procedures, and definitions might become significant in individual patients treated by multiple providers. That being said, other, easier to measure pathological features (e.g. PNI, ENE, and LVI), should also be considered in a modified head and neck CSCC staging system; however, DOI has considerable correlation with these features, making their inclusion less meaningful and the modified staging system cumbersome.

This study had some limitations. First, we used retrospectively collected data, and the physicians did not assign treatment in a randomized fashion. Second, external validation of our proposed system prior to considering implementation in practice is required. Third, we could not exclude the possibility that the value DOI differs among subsites in the head and neck [15]. Fourth, we limited our study population to patients undergoing surgery at a large academic cancer center. Therefore, our data set may not have included patients with early-stage lesions who underwent excision at another facility or by a local provider. However, the majority of these lesions are likely to be very early (<5 mm) tumors [16], and we actually expect that their inclusion will enhance our proposed model's performance.

In conclusion, our results showed that DOI provides prognostic information complementary to the current AJCC T classification in patients with head and neck CSCC treated with surgical resection. Similar to mucosal HNSCC, the proposed model (model 6) should be externally validated, which is the next step towards incorporation in the AJCC, and better stratification into different prognoses categories potentially necessitating disparate treatment and/or surveillance.

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None.

Author contributions

Moran Amit: Concept; acquisition and performance of the analysis; drafting of the manuscript, tables, and figures; responsibility for the overall content; and review of the final document and approval for publication. Priyadharsini Nagarajan, Anshu Khanna, Liu Chuan: Data acquisition, and review of the final document and approval for publication. Avi Benov, Frederico Netto, and Samantha Tam: Substantial contributions to the acquisition and performance of the analysis and review of the final document and approval for publication. Adel El-Naggar, Amy Moreno, David Rosenthal, Bonnie Glisson, Renata Ferrarotto, Michael Wong, Michael Migden, Goujun Li, Ryan Goepfert, Randal S. Weber and Jeffrey N. Myers: Concept and review of the final document and approval for publication. Neil Gross: Concept; drafting of the manuscript, tables, and figures; responsibility for the overall content; and review of the final document and approval for publication.

Conflict of interest statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.11.019.

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