Prediction of Poor Outcome for Cutaneous Squamous Cell Carcinoma of the Head and Neck Comparing Classification Systems

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Prediction of Poor Outcome for Cutaneous Squamous Cell Carcinoma of the Head and Neck Comparing Classification Systems: A Competing Risk Analysis

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TO THE EDITOR

The most commonly used staging system for cutaneous squamous cell carcinoma (cSCC) of the head and neck is the American Joint Committee on Cancer eighth edition (AJCC8) system (NVDV, 2018; Stratigos et al., 2020). This system is predominantly based on tumor size in lower stages and extradermal or perineural invasion in higher stages. An alternative classification system for cSCC on all locations is the Brigham and Women's Hospital (BWH) classification system (Jambusaria-Pahlajani et al., 2013). This system is based on high-risk factors derived from tumor characteristics. The more high-risk factors the tumor presents, the higher the stage. An important difference between the systems is that a tumor can be staged as AJCC8 T3 on the basis of one risk factor (perineural invasion or deep invasion), whereas one risk factor leads to a BWH T2a stage (Supplementary Table S1). Recent studies suggest a better prognostic value of BWH classification system than AJCC8 system; however, larger cohort data are lacking (Blechman et al., 2019; Cañueto et al., 2019; Roscher et al., 2018; Ruiz et al., 2019). Our aim was to analyze which classification system predicts outcome better in a larger cohort.

Patients from the University Medical Center Groningen with primary cSCC of the head and neck without nodal or distant metastasis at diagnosis, diagnosed between 1 January 2000 and 1 January 2014 were retrospectively included (N = 748). Because survival analyses were performed with death as a competing risk, the analyses were performed at the patient level. A total of 748 patients in our cohort had 1,087 tumors. The tumor with poor outcome or the highest stage was chosen as the index tumor. In case of poor outcome with uncertainty about the culprit tumor patients were discussed in our research group. Histopathology was reassessed if data were missing. Patient and tumor characteristics were summarized using descriptive statistics. The proportion of high-stage and low-stage tumors per classification system was compared with chi-squared tests. Competing risk analyses were performed to account for the risk of dying before developing poor outcome. Cumulative incidence functions (Lambert, 2017) are presented for combined poor outcome (CPO), comprising local recurrence, nodal metastasis, and distant metastasis, and for these events separately. To compare the predictive accuracy of the staging systems for CPO, time-dependent area under the curve (AUC) estimates with death as a competing risk were calculated in R (R Core Team, 2021) with the methods implemented in the time-receiver operating characteristic package (Blanche et al., 2013). The AUC can be used to compare the accuracy and can be interpreted as a concordance index, meaning the AUC is equal to the probability that the staging of a random patient with poor outcome is higher than the staging of a random patient without poor outcome (Blanche et al., 2013). Statistical analyses were performed using STATA (version 14.2; StataCorp, College Station, TX) and R (version 4.0.1; The R Foundation for Statistical Computing, Vienna, Austria).

Patient and tumor characteristics are shown in Supplementary Table S2. More patients were classified as high-stage (T3 or higher for AJCC8 and T2b or higher for BWH) by AJCC8 system (20.9%) than by BWH classification system (14.3%, $P < 0.001$), without identifying more poor outcomes: 28.2% of high-stage AJCC8 tumors developed CPO than 31.8% of high-stage BWH tumors. On the contrary, low-stage AJCC8 tumors developed CPO in 7.9% than 8.9% in BWH low-stage tumors (Supplementary Table S3). Both AJCC8 and BWH classification systems showed an increasing percentage of patients with lower recurrence, nodal metastasis distant metastasis, and CPO with increasing T stage (Table 1 and Supplementary Tables S4–6). The frequencies of CPO, no CPO, death, and censored cases are shown in Table 2 for each time point. At 60 months, 88 patients (11.8%) had developed CPO. Table 2 also displays the AUC estimates with 95% confidence interval. The AUC estimate was significantly higher for BWH classification system at 24, 36, 48, and 60 months than to AJCC8 system. Supplementary Figure S1 shows the time-dependent receiver operating characteristic curve at 60 months for AJCC8 system in red and for BWH classification system in blue, with a significant higher prognostic value for BWH classification system ($P = 0.018$).

This study shows slightly more appropriate classifications and higher prognostic value for BWH classification system than for AJCC8 system. Recent studies comparing AJCC8 and BWH classification systems with different methodologies also show that both staging systems show more poor outcomes with increasing stage

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; AUC, area under the curve; BWH, Brigham and Women's Hospital; CPO, combined poor outcome; cSCC, cutaneous squamous cell carcinoma

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Table 1. CIF for Progression of Disease (Comprising Local Recurrence, Nodal Metastasis, and Distant Metastasis) by Staging System with Death as Competing Risk

Tumor Stage	t = 12	t = 24	t = 36	t = 48	t = 60
AJCC8, CIF (95% CI)					
T1	0.028 (0.016–0.045)	0.042 (0.027–0.062)	0.044 (0.029–0.065)	0.051 (0.034–0.073)	0.061 (0.042–0.084)
T2	0.143 (0.076–0.230)	0.172 (0.097–0.264)	0.187 (0.108–0.283)	0.204 (0.120–0.303)	0.204 (0.120–0.303)
T3	0.231 (0.167–0.302)	0.266 (0.198–0.340)	0.288 (0.217–0.363)	0.288 (0.217–0.363)	0.288 (0.217–0.363)
T4	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)
BWH, CIF (95% CI)					
T1	0.023 (0.012–0.039)	0.034 (0.020–0.053)	0.034 (0.020–0.053)	0.041 (0.025–0.061)	0.051 (0.033–0.074)
T2a	0.156 (0.103–0.219)	0.185 (0.126–0.251)	0.207 (0.145–0.277)	0.215 (0.152–0.286)	0.215 (0.152–0.286)
T2b	0.242 (0.160–0.334)	0.288 (0.198–0.383)	0.300 (0.209–0.396)	0.300 (0.209–0.396)	0.300 (0.209–0.396)
T3	0.413 (0.150–0.661)	0.497 (0.206–0.733)	0.580 (0.268–0.799)	0.580 (0.268–0.799)	0.580 (0.268–0.799)

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; CI, confidence interval; CIF, cumulative incidence function; t, time in months.

(Blechman et al., 2019; Cañueto et al., 2019; Ruiz et al., 2019). One study describes that more tumors were classified as high-stage by AJCC8 system than with BWH classification system, without identifying more poor outcomes, predominantly because of a similar risk of poor outcome between AJCC8 T2 and T3 tumors. This suggests that BWH classification system more accurately identifies high-risk tumors (Ruiz et al., 2019). AJCC8 system leading to higher staging in this study and previous studies is probably the result of only one risk factor being necessary for upstaging, whereas this is not the case for BWH classification system (Cañueto et al., 2019; Ruiz et al., 2019). A case-control study on 6,721 patients with cSCC showed a higher sensitivity, specificity, number of correctly classified tumors, and concordance index for BWH classification system than for AJCC8 system, comparable to our findings (Roscher et al., 2018).

The demonstrated AUC value of 0.74 for BWH classification system shows that there is still room for improvement (Mandrekar, 2010). The risk factors taken into account by BWH classification system greatly correspond to the risk factors with the highest risk ratio for recurrence, metastasis, or disease-specific death (Thompson et al., 2016). Future investigations to improve the prognostic accuracy of staging systems might explore the inclusion of tumor characteristics on a molecular level or patient characteristics such as immune status or age.

Limitations of this study are its retrospective nature and the single center setup. Furthermore, because we selected the tumor with the highest stage in patients with multiple tumors, low-stage tumors might be underrepresented in our study. Because AJCC8 and BWH classification systems were compared using the same underlying data, the comparison will not be affected by this choice.

The major strength of this study is that all missing histopathological data were reassessed by one dermatopathologist. Furthermore, data of a large cohort were analyzed, with detailed statistics accounting for the risk of dying in this elderly population.

To conclude, classification of cSCC of the head and neck on the basis of cumulative number of risk factors, such as by BWH classification system, gives a slightly more accurate prediction of outcome than AJCC8 system. We therefore suggest using BWH classification system in clinical practice, also because a system of adding risk factors might be easier to use.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, AJGL. The data are not publicly available due to information that could compromise the privacy of research participants.

Table 2. Comparison of the AUC of AJCC8 and BWH at 12, 24, 36, 48, and 60 months (N = 748)

Tumor Stage		t = 12	t = 24	t = 36	t = 48	t = 60
CPO, n (%)		61 (8.2)	75 (10.0)	80 (10.7)	84 (11.2)	88 (11.8)
No poor outcome, n (%)		588 (78.6)	507 (67.8)	431 (57.6)	364 (48.7)	287 (38.4)
Death, n (%)		56 (7.5)	110 (14.7)	155 (20.7)	199 (26.6)	226 (30.2)
Censored, n (%)		43 (5.7)	56 (7.5)	82 (11.0)	101 (13.5)	147 (19.7)
AUC, estimate (95% CI)	AJCC8	0.77 (0.71–0.83)	0.74 (0.69–0.80)	0.75 (0.69–0.80)	0.73 (0.63–0.78)	0.71 (0.65–0.76)
	BWH	0.79 (0.73–0.84)	0.77 (0.72–0.83)	0.78 (0.73–0.83)	0.76 (0.71–0.81)	0.74 (0.68–0.79)
	P-value	0.279	**0.039**	**0.024**	**0.026**	**0.018**

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; AUC, area under the curve; BWH, Brigham and Women's Hospital; CI, confidence interval; CPO, combined poor outcome; H_0, null hypothesis; t = time in months.

Estimates, CIs and *P*-values of the test of H_0: $AUC_{AJCC8}(t) = AUC_{BWH}(t)$.

CPO consists of local recurrence of the tumor, nodal metastasis, and distant metastasis.

Three patients developed CPO after 60 months.

Censored patients did not develop CPO but had a shorter follow-up than the respective time point.

Significant *P*-values are in bold.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: BACvD, ER, MSvK, BECP, GBH, AJGL; Data Curation: AJGL, GFHD; Formal Analysis: AJGL, BACvD; Investigation: AJGL, BACvD, DP, ER, MSvK; Methodology: BACvD, DP, AJGL, MSvK; Project Administration: AJGL; Supervision: BACvD, ER, MSvK; Validation: BACvD, MSvK, AJGL; Visualization: AJGL; Writing - Original Draft Preparation: AJGL; Writing - Review and Editing: AJGL, BACvD, DP, BECP, GBH, GFHD, ER, MSvK

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.02.015.

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Spectrum and Incidence of Skin Cancer among Individuals with Li-Fraumeni Syndrome

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TO THE EDITOR

Li-Fraumeni syndrome (LFS) is a hereditary cancer predisposition syndrome primarily caused by germline pathogenic variants in the *TP53* tumor suppressor gene. Individuals with LFS have an increased risk of multiple cancers over the lifetime, with a risk of at least one cancer approaching 70–100% by age 60 years (Mai et al., 2016; Malkin, 2011). Patients with LFS undergo intensive cancer screening centered around whole-body magnetic resonance imaging (National Comprehensive Cancer Network, 2021).

Annual whole-body skin examinations are recommended for individuals with LFS, but this recommendation is

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; LFS, Li-Fraumeni syndrome; SCC, squamous cell carcinoma; SIR, standardized incidence ratio

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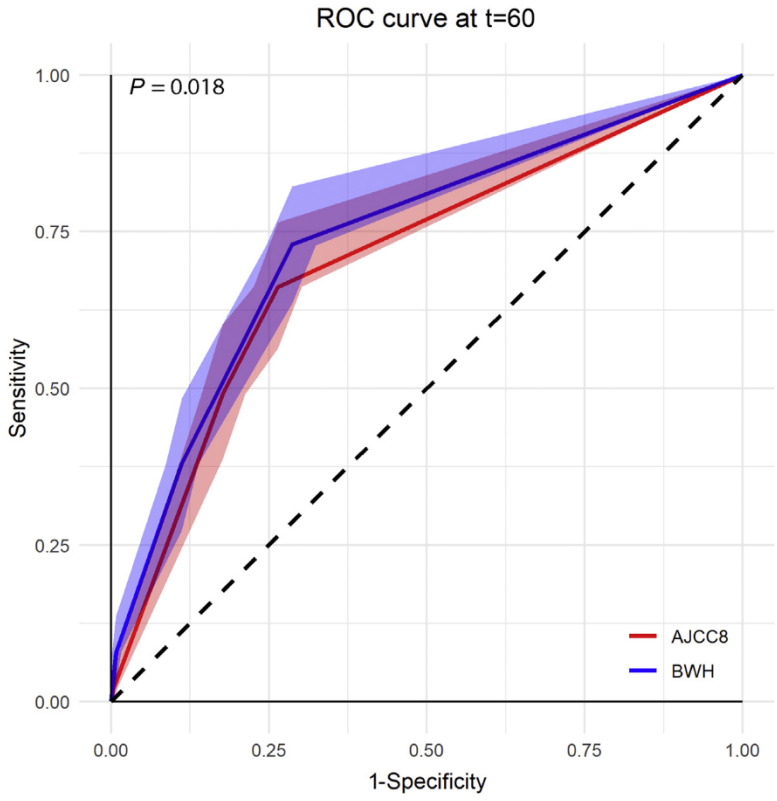

Supplementary Figure S1. Time-dependent ROC curves with competing risks estimated by inverse probability of censoring weighting estimators (KM-weights) at t = 60 for AJCC8 (red) and BWH (blue) with POD as outcome measure including 95% confidence intervals. AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; KM, Kaplan–Meier; POD, progression of disease, comprising local recurrence, nodal metastasis, and distant metastasis; ROC, receiver operating characteristic; t, time in months.

Supplementary Table S1. Overview of Staging Criteria for AJCC8 and BWH

Tumor Stage	Characteristics
AJCC8	
T1	Tumor smaller than 2 cm in greatest dimension
T2	Tumor 2 cm or larger, but smaller than 4 cm in greatest dimension
T3	Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion[1]
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
BWH	
High-risk factors	Tumor diameter ≥2 cm, poor differentiation, perineural invasion ≥0.1 mm, tumor invasion beyond subcutaneous fat
T1	0 high-risk factors
T2a	1 high-risk factor
T2b	2–3 high-risk factors
T3	4 high-risk factors or bone invasion

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital.

[1]Deep invasion is defined by the AJCC as invasion beyond the subcutaneous fat or >6 mm. Perineural invasion is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Supplementary Table S2. Patient and Tumor Characteristics (N = 748)

Characteristics	Total (N = 748)
Median age, y (range)	74 (25–105)
Sex, n (%)	
Men	499 (66.7)
Women	249 (33.3)
Median follow-up time, mo (range)	53 (1–206)
Immunosuppression, n (%)	128 (17.1)
Tumor diameter, n (%)	
<2 cm	575 (76.9)
≥2 cm and <4 cm	129 (17.3)
≥4 cm	44 (5.9)
Tumor differentiation, n (%)	
Well	324 (43.3)
Moderate	362 (48.4)
Poor	61 (8.2)
Unknown	1 (0.1)
Invasion depth, n (%)	
≤6 mm	662 (88.5)
≤6 mm and extradermal invasion (beyond subcutaneous fat)	32 (4.3)
>6 mm	86 (11.5)
>6 mm and extradermal invasion (beyond subcutaneous fat)	23 (3.1)
Perineural invasion, n (%)	68 (9.1)
T stage (AJCC8), n (%)	
T1	512 (68.5)
T2	80 (10.7)
T3	152 (20.3)
T4[1]	4 (0.5)
T stage (BWH), n (%)	
T1	489 (65.4)
T2a	152 (20.3)
T2b	94 (12.6)
T3	13 (1.7)

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital.

Perineural invasion was observed in nerves of ≥0.1 mm in caliber in all cases.

[1]AJCC8 T4 comprises patients with a T4a tumor (N = 3) and a T4b tumor (N = 1).

Supplementary Table S3. Poor Outcome Per T Stage (N = 748)

Tumor Stage	LR	NM	DM	POD	Total
AJCC8 T stage, n (%)					
T1	24 (4.7)	9 (1.8)	1 (0.2)	32 (6.3)	512
T2	6 (7.5)	12 (15.0)	1 (1.3)	15 (18.8)	80
T3	25 (16.5)	26 (17.1)	8 (5.3)	42 (27.6)	152
T4[1]	1 (25.0)	2 (50.0)	1 (25.0)	2 (50.0)	4
BWH T stage, n (%)					
T1	19 (3.9)	6 (1.2)	1 (0.2)	26 (5.3)	489
T2a	16 (10.5)	22 (14.5)	4 (2.6)	31 (20.4)	152
T2b	18 (19.2)	16 (17.0)	4 (4.3)	27 (28.7)	94
T3	3 (23.1)	5 (38.5)	2 (15.4)	7 (53.9)	13
Total, n (%)	56 (7.5)	49 (6.6)	11 (1.5)	91 (12.2)	

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; DM, distant metastasis; LR, local recurrence; NM, nodal metastasis; POD, progression of disease, comprising local recurrence, nodal metastasis, and distant metastasis.

Due to some patients having multiple poor outcomes, the number of patients with POD is lower than when the numbers of LR, NM, and DM are added together.

[1]AJCC8 T4 comprises patients with a T4a tumor (N = 2) and a T4b tumor (N = 1).

Supplementary Table S4. CIF for Local Recurrence by Staging System with Death as Competing Risk

Tumor Stage	t = 12	t = 24	t = 36	t = 48	t = 60
AJCC8, CIF (95% CI)					
T1	0.016 (0.008–0.030)	0.028 (0.016–0.046)	0.032 (0.019–0.051)	0.039 (0.024–0.059)	0.046 (0.030–0.068)
T2	0.053 (0.017–0.120)	0.068 (0.025–0.140)	0.068 (0.025–0.140)	0.084 (0.034–0.163)	0.084 (0.034–0.163)
T3	0.116 (0.071–0.174)	0.144 (0.093–0.206)	0.173 (0.116–0.239)	0.173 (0.116–0.239)	0.173 (0.116–0.239)
T4	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)
BWH, CIF (95% CI)					
T1	0.013 (0.005–0.026)	0.023 (0.012–0.040)	0.023 (0.012–0.040)	0.030 (0.017–0.049)	0.038 (0.023–0.059)
T2a	0.069 (0.035–0.117)	0.083 (0.045–0.135)	0.105 (0.062–0.162)	0.113 (0.068–0.172)	0.113 (0.068–0.172)
T2b	0.144 (0.081–0.224)	0.177 (0.107–0.263)	0.201 (0.125–0.289)	0.201 (0.125–0.289)	0.201 (0.125–0.289)
T3	0.083 (0.005–0.311)	0.167 (0.027–0.413)	0.250 (0.060–0.505)	0.250 (0.060–0.505)	0.250 (0.060–0.505)

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; CI, confidence interval; CIF, cumulative incidence function; t, time in months.

Supplementary Table S5. CIF for Nodal Metastasis by Staging System with Death as Competing Risk

Tumor Stage	t = 12	t = 24	t = 36	t = 48	t = 60
AJCC8, CIF (95% CI)					
T1	0.010 (0.004–0.022)	0.014 (0.006–0.028)	0.014 (0.006–0.028)	0.014 (0.006–0.028)	0.016 (0.008–0.031)
T2	0.103 (0.048–0.182)	0.131 (0.067–0.216)	0.146 (0.078–0.236)	0.162 (0.089–0.256)	0.162 (0.089–0.256)
T3	0.156 (0.103–0.219)	0.177 (0.120–0.243)	0.177 (0.120–0.243)	0.177 (0.120–0.243)	0.177 (0.120–0.243)
T4	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)	0.500 (0.058–0.845)
BWH, CIF (95% CI)					
T1	0.008 (0.003–0.020)	0.008 (0.003–0.020)	0.008 (0.003–0.020)	0.008 (0.003–0.020)	0.011 (0.004–0.024)
T2a	0.108 (0.065–0.164)	0.136 (0.087–0.197)	0.144 (0.093–0.206)	0.152 (0.099–0.215)	0.152 (0.099–0.215)
T2b	0.143 (0.803–0.223)	0.177 (0.107–0.262)	0.177 (0.107–0.262)	0.177 (0.107–0.262)	0.177 (0.107–0.262)
T3	0.413 (0.150–0.661)	0.413 (0.150–0.661)	0.413 (0.150–0.661)	0.413 (0.150–0.661)	0.413 (0.150–0.661)

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; CI, confidence interval; CIF, cumulative incidence function; t, time in months.

Supplementary Table S6. CIF for Distant Metastasis by Staging System with Death as Competing Risk

Tumor Stage	t = 12	t = 24	t = 36	t = 48	t = 60
AJCC8, CIF (95% CI)					
T1	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)
T2	0.014 (0.001–0.065)	0.014 (0.001–0.065)	0.014 (0.001–0.065)	0.014 (0.001–0.065)	0.014 (0.001–0.065)
T3	0.027 (0.009–0.063)	0.055 (0.026–0.101)	0.055 (0.026–0.101)	0.055 (0.026–0.101)	0.055 (0.026–0.101)
T4	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)	0.250 (0.009–0.665)
BWH, CIF (95% CI)					
T1	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)	0.002 (0.000–0.011)
T2a	0.014 (0.003–0.045)	0.028 (0.009–0.065)	0.028 (0.009–0.065)	0.028 (0.009–0.065)	0.028 (0.009–0.065)
T2b	0.022 (0.004–0.069)	0.044 (0.014–0.101)	0.044 (0.014–0.101)	0.044 (0.014–0.101)	0.044 (0.014–0.101)
T3	0.167 (0.027–0.413)	0.167 (0.027–0.413)	0.167 (0.027–0.413)	0.167 (0.027–0.413)	0.167 (0.027–0.413)

Abbreviations: AJCC8, American Joint Committee on Cancer eighth edition; BWH, Brigham and Women's Hospital; CI, confidence interval; CIF, cumulative incidence function; t, time in months.