Comparison of tumor staging systems for cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia

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Background: Patients with chronic lymphocytic leukemia (CLL) are at increased risk for poor outcomes as a result of cutaneous squamous cell carcinoma (CSCC).

Objective: To compare the relative effectiveness of tumor staging systems for CSCC in a well-defined cohort of patients with CLL.

Methods: This retrospective outcomes study included 454 CSCC tumors among 161 patients with underlying CLL who were evaluated at a single academic medical center. Each tumor was staged according to Brigham and Women's Hospital (BWH), Union for International Cancer Control eighth edition (UICC8), and American Joint Committee on Cancer seventh edition (AJCC7) and eighth edition (AJCC8) criteria. We compared the effectiveness of tumor risk stratification according to each system.

Results: The BWH tumor staging system demonstrated superior risk stratification relative to the AJCC7 criteria (C-index, 0.725 vs 0.615; $P = .036$) and trended toward improved stratification relative to the AJCC8 (C-index, 0.796 vs 0.732; $P = .214$) and UICC8 (C-index, 0.725 vs 0.636; $P = .096$) staging systems.

Limitations: Our study must be interpreted in the context of its retrospective design and relatively small number of adverse outcomes available for statistical analysis.

Conclusions: The BWH system outperformed the AJCC7 criteria and trended toward superior risk stratification relative to both the AJCC8 and UICC8 criteria. (J Am Acad Dermatol 2019;80:639-45.)

Key Words: American Joint Committee on Cancer; Brigham and Women's Hospital; chronic lymphocytic leukemia; squamous cell carcinoma; staging; system; tumor; Union for International Cancer Control.

Chronic lymphocytic leukemia (CLL) is a B-cell lymphoproliferative disorder and the most prevalent adult leukemia in the United States.[1] There is a well-established association between CLL and secondary cancers, with skin carcinoma being the most common.[2] Cutaneous malignancies have a higher risk of adverse outcomes in patients with CLL than in the general population.[3,4] For cutaneous squamous cell carcinoma (CSCC), the rate of local recurrence (LR) following Mohs micrographic surgery has been estimated to be 13.4% in patients with CLL, which is far higher than the 3% rate observed in the general population.[5] In addition, CSCC may have higher rates of nodal metastasis (NM) and disease-specific death (DSD) in patients with CLL than in the general population.[6,7]

Two of the most commonly used tumor staging systems for CSCC are the American Joint Committee

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on Cancer (AJCC) and the Union for International Cancer Control (UICC) criteria. In 2013, the Brigham and Women's Hospital (BWH) tumor staging system for CSCC was proposed with the goal of risk-stratifying the T2 tumor category of the AJCC seventh edition (AJCC7), which was noted to be heterogeneous and contain the majority of poor patient outcomes.[8] A validation study performed at the same institution showed superior risk stratification according to the BWH system relative to both the AJCC7 and UICC seventh edition (UICC7) criteria.[9] Several smaller studies by other research groups have also reported superior T2 risk stratification according to the BWH criteria, but these findings have not been validated in a large cohort of patients with CLL.[10,11]

CAPSULE SUMMARY

- Patients with chronic lymphocytic leukemia are at increased risk for poor outcomes of cutaneous squamous cell carcinoma.
- The Brigham and Women's Hospital tumor staging system offers superior risk stratification for cutaneous squamous cell carcinoma in patients with underlying chronic lymphocytic leukemia in a well-defined patient cohort.

In 2017, the AJCC eighth edition (AJCC8) and UICC eighth edition (UICC8) were published and include several changes to previous staging criteria for CSCC.[12,13] Histologic grade and location on the ear or vermillion lip are no longer considered in the staging of CSCC tumors according to these 2 systems. In addition, tumor invasion beyond the subcutaneous fat is no longer required for staging into the T3 category. Instead, perineural invasion or maximum tumor dimension beyond defined thresholds are sufficient for T3 staging. In addition, the AJCC8 criteria for CSCC apply only to tumors located on the head or neck.

The present study evaluates and compares the effectiveness of CSCC tumor risk stratification for the AJCC7, AJCC8, UICC8, and BWH tumor staging systems in a well-defined cohort of patients with underlying CLL. The adverse outcomes considered in this study include rates of LR, NM, and DSD associated with CSCC.

METHODS

The present study received approval from the institutional review board at the Mayo Clinic.

Study design

This retrospective outcomes study utilized an electronic database of patients in whom CLL had been diagnosed between January 1, 1995, and January 1, 2016, at the Mayo Clinic in Rochester, Minnesota. This database was queried for cases of primary CSCC that developed after an initial diagnosis of CLL. Exclusion criteria included squamous cell carcinoma (SCC) in situ, noncutaneous SCC, non-primary SCC, eyelid or anogenital primary tumor sites, cases with insufficient documentation for SCC tumor staging, and SCC tumors that developed before the diagnosis of CLL. Tumors developing after a bone marrow transplant were included, and a subgroup analysis indicated that this did not affect the major findings and conclusions of this study. Additional pertinent SCC tumor characteristics (eg, primary tumor site, depth of invasion, tumor differentiation, perineural invasion) were collected through a detailed review of each medical record, as were details regarding the outcomes of LR, NM, and DSD. Each CSCC tumor was then staged according to the AJCC7, AJCC8, UICC8, and BWH criteria.

Statistical analysis

These staging criteria were evaluated with respect to event-free survival (EFS), which was defined as the time from CSCC diagnosis to LR, NM, or DSD. Patients without an event were censored at the date of last known follow-up with dermatology, hematology, or primary care at the Mayo Clinic through January 1, 2017. EFS data were evaluated by using the Kaplan-Meier method and Cox regression with adjustment for age and sex. For each EFS model we generated the C-index, which is a probability of concordance between predicted and observed survival, with C equal to 0.5 for random predictions and C equal to 1 for a perfectly discriminating model. The staging system with the highest C-index was considered to outperform the other staging criteria. A statistical test to compare the C-index was derived by using the R software package compareC, with a P value less than .05 considered to be statistically significant.[14]

RESULTS

Patient and tumor characteristics

The Mayo Clinic database was queried to identify 161 patients with CLL with 454 qualifying CSCC tumors during the period from 1995 to 2016. The median age at CLL diagnosis was 67 years, and 83% of the patients were male, which is representative of a typical population of patients with CLL (Tables I-III). The majority of primary CSCC tumors occurred on the

Abbreviations used:

AJCC: American Joint Committee on Cancer
AJCC7: American Joint Committee on Cancer seventh edition
AJCC8: American Joint Committee on Cancer eighth edition
BWH: Brigham and Women's Hospital
CLL: chronic lymphocytic leukemia
CSCC: cutaneous squamous cell carcinoma
DSD: disease-specific death
EFS: event-free survival
LR: local recurrence
NM: nodal metastasis
SCC: squamous cell carcinoma
UICC8: Union for International Cancer Control eighth edition

head and neck (62%), were well differentiated (59%), and were less than 2 cm in the largest dimension (84%). The median depth was 3 mm among the 39 cases with this parameter documented in pathology reports. No tumors were staged as T3 or higher according to the BWH and AJCC7 criteria. Among this cohort, there were 12 cases of LR, 5 cases of NM, and 3 cases of DSD. With a median follow-up of 2.6 years (range, 0-16.7), the cumulative incidence rate for time to LR at 1 year was 1.6% (95% confidence interval, 0.8%-3.4%) and at 3 years it was 3.0% (95% confidence interval,1.75%-5.3%). All 3 cases of DSD were attributable to locally invasive or metastatic CSCC resulting from head or neck primary tumor sites. The majority of adverse outcomes related to SCC tumors occurred in patients at Rai stages III and IV (high-risk Rai stages).

Staging systems associated with CSCC outcome

All 3 staging systems were significantly associated ($P < .05$) with CSCC outcome after adjustment for age and sex (Table IV).

Comparison of AJCC7, UICC8, and BWH criteria

The BWH criteria outperformed the AJCC7 criteria (C-index, 0.725 vs 0.615; $P = .036$) and trended toward superior performance over the UICC8 criteria (C-index, 0.725 vs 0.636; $P = .096$), as summarized in Table V. Among tumors staged as T1 according to the AJCC7 criteria, 26 (7%) were up-staged according to the criteria to T2a. Among the up-staged tumors, there were 2 cases of LR, 3 cases of NM, and 1 DSD (Table VI). Among the tumors staged T2 according to the AJCC7 criteria 9 (14%) were up-staged according to the BWH criteria from T2a to T2b, whereas 4 tumors were down-staged to T1. There were 2 cases of LR, 1 NM, and 2 DSDs among the up-staged tumors, whereas no adverse outcomes occurred among the down-staged tumors.

For tumors staged T1 according to the UICC8 criteria, 30 (8%) were up-staged according to the BWH system as T2a, and among these up-staged tumors there were 2 cases of LR, 3 cases of NM, and 1 DSD. No adverse outcomes occurred in the 2 tumors up-staged as T2b. Among T2 tumors according to the UICC criteria, 2 were staged T2b according to the

Table I. Patient characteristics (N = 161)

Characteristics	Value
Age at CLL Dx, y	
Mean (SD)	66.6 (9.6)
Median (IQR)	67.0 (61.0, 73.0)
Time from CLL Dx to first CSSC, y	
Mean (SD)	5.2 (3.6)
Median (IQR)	4.8 (2.7-7.7)
Follow-up from first CSSC, y	
Mean (SD)	4.0 (3.6)
Median (IQR)	3.1 (1.5-5.1)
Sex	
Male	134 (83.2%)
Race	
White	157 (97.5%)
Not disclosed	1 (0.6%)
Unknown	3 (1.9%)
Rai stage at CLL Dx*	
Stage 0	73 (49.7%)
Stage 1 or 2	67 (45.6%)
Stage 3 or 4	7 (4.8%)
Transplant (bone marrow/stem cell)	
Transplant	9 (5.6%)

CLL, Chronic lymphocytic leukemia; *CSSC*, cutaneous squamous cell carcinoma; *Dx*, diagnosis; *IQR*, interquartile range; *SD*, standard deviation.
*Data not available for all patients.

Table II. Stratification according to Rai stage

Model	n (events)	HR (95% CI)	*P* value
BWH			
Rai 0/I/II	173 (3)	5.4 (1.2-23.6)	.026
Rai III/IV	219 (7)	9.6 (2.7-33.6)	<.001
AJCC7			
Rai 0/I/II	173 (3)	2.5 (0.2-27.8)	.457
Rai III/IV	219 (7)	5.3 (1.2-23.7)	.030
UICC			
Rai 0/I/II	173 (3)	3.8 (0.9-16.3)	.077
Rai III/IV	219 (7)	4.8 (1.7-13.6)	.003
AJCC8			
Rai 0/I/II	111 (3)	2.4 (0.5-10.8)	.257
Rai III/IV	132 (6)	4.4 (1.5-12.7)	.006

AJCC7, American Joint Committee on Cancer seventh edition; *AJCC8*, American Joint Committee on Cancer eighth edition; *BWH*, Brigham and Women's Hospital; *HR*, hazard ratio; *UICC*, Union for International Cancer Control.

Table III. Tumor characteristics

Characteristics	Any poor outcome (n = 15)	No poor outcome (n = 439)	Total (N = 454)
Primary tumor laterality			
Left	8 (53.3%)	214 (48.7%)	222 (48.9%)
Right	4 (26.7%)	191 (43.5%)	195 (43.0%)
Midline	3 (20.0%)	34 (7.7%)	37 (8.1%)
Maximum tumor dimension			
Max dimension <2 cm	7 (46.7%)	374 (85.2%)	381 (83.9%)
Max dimension ≥2 cm	8 (53.3%)	65 (14.8%)	73 (16.1%)
Differentiation*			
Not reported	1 (6.7%)	103 (23.5%)	104 (23.0%)
Well differentiated	8 (53.3%)	258 (58.9%)	266 (58.7%)
Moderately differentiated	3 (20.0%)	51 (11.6%)	54 (11.9%)
Poorly differentiated	2 (13.3%)	12 (2.7%)	14 (3.1%)
Desmoplastic	0 (0.0%)	1 (0.2%)	1 (0.2%)
Acantholytic	0 (0.0%)	11 (2.5%)	11 (2.4%)
Sarcomatoid	1 (6.7%)	1 (0.2%)	2 (0.4%)
Clear cell change	0 (0.0%)	1 (0.2%)	1 (0.2%)
Tumor location			
Non–head and/or neck	4 (26.7%)	169 (38.5%)	173 (38.1%)
Head and/or neck	11 (73.3%)	270 (61.5%)	281 (61.9%)
Poor outcomes			
Local recurrence	12 (80.0%)	0 (0.0%)	12 (2.6%)
Nodal metastasis	5 (33.3%)	0 (0.0%)	5 (1.1%)
Disease-specific death	3 (20.0%)	0 (0.0%)	3 (0.7%)
AJCC7 stage			
T1	9 (60.0%)	381 (86.8%)	390 (85.9%)
T2	6 (40.0%)	58 (13.2%)	64 (14.1%)
AJCC8 stage			
T1	4 (36.4%)	227 (84.1%)	231 (82.2%)
T2	4 (36.4%)	34 (12.6%)	38 (13.5%)
T3	3 (27.3%)	9 (3.3%)	12 (4.3%)
UICC stage			
T1	9 (60.0%)	391 (89.1%)	400 (88.1%)
T2	3 (20.0%)	42 (9.6%)	45 (9.9%)
T3	3 (20.0%)	6 (1.4%)	9 (2.0%)
BWH stage			
T1	5 (33.3%)	363 (82.7%)	368 (81.1%)
T2a	8 (53.3%)	69 (15.7%)	77 (17.0%)
T2b	2 (13.3%)	7 (1.6%)	9 (2.0%)

AJCC7, American Joint Committee on Cancer seventh edition; *AJCC8*, American Joint Committee on Cancer eighth edition; *BWH*, Brigham and Women's Hospital; *UICC*, Union for International Cancer Control.
*Data not available for all patients.

BWH criteria, but no adverse outcomes occurred in this up-staged group. Four of the UICC T3 tumors were down-staged as T2a, with 1 resulting in LR. Kaplan-Meier curves illustrating EFS for the BWH, AJCC7, and UICC8 tumor staging systems are shown in Fig 1.

Comparison of AJCC7, AJCC8, and BWH criteria

Primary CSCC tumors occurring at locations outside the head or neck were excluded from this portion of the analysis to allow comparison of the AJCC7, AJCC8, and BWH criteria. The AJCC8 tumor staging system trended toward superior performance relative to the AJCC7 criteria (C-index, 0.732 vs 0.690; $P = .242$).

The BWH system resulted in upstaging 9 (4%) of the AJCC8 T1 tumors into the higher-risk T2a category. These up-staged tumors included 1 case of LR, 2 cases of NM, and 1 DSD. Among the tumors staged T2 according to the AJCC8 criteria, no adverse events occurred in the 3 tumors that were up-staged into the T2b category. The BWH system trended toward superior performance relative to the AJCC8 criteria (C-index, 0.796 vs 0.732; $P = .214$) when all poor outcomes were included in the analysis

Table IV. Association of tumor staging systems with poor CSCC outcomes after adjustment for age and sex

Model and stage	n (events)	HR (95% CI)	*P* value
BWH			
T1	368 (5)	Ref	Ref
T2a	77 (8)	8.6 (2.8-26.3)	.0002
T2b	9 (2)	12.9 (2.5-66.5)	.0023
AJCC7			
T1	390 (9)	Ref	Ref
T2	64 (6)	4.4 (1.5-12.4)	.0050
UICC			
T1	400 (9)	Ref	Ref
T2	45 (3)	3.8 (1.03-14.3)	.0458
T3	9 (3)	19.7 (5.2-74.0)	<.0001
AJCC8			
T1	231 (4)	Ref	Ref
T2	38 (4)	5.9 (1.5-23.5)	.0125
T3	12 (3)	15.1 (3.4-67.9)	.0004

AJCC7, American Joint Committee on Cancer seventh edition; *AJCC8*, American Joint Committee on Cancer eighth edition; *BWH*, Brigham and Women's Hospital; HR, hazard ratio; Ref, reference; *UICC*, Union for International Cancer Control.

Table V. Comparison of tumor staging systems

Comparative staging system	Comparative C-index	BWH C-index	*P* value
AJCC7	0.615	0.725	.036
UICC8	0.636	0.725	.096
AJCC8	0.732	0.796	.214

AJCC7, American Joint Committee on Cancer seventh edition; *AJCC8*, American Joint Committee on Cancer eighth edition; *BWH*, Brigham and Women's Hospital; *UICC*, Union for International Cancer Control.

(Table V and Fig 2). Similar results were seen for the outcomes of LR or NM.

DISCUSSION

In the present study, we have compared the AJCC7, AJCC8, UICC8, and BWH tumor staging systems for CSCC in a well-defined cohort of patients with CLL. To our knowledge, this is the largest study to date evaluating tumor staging systems for CSCC in patients with underlying CLL. Given that this patient population is at significantly increased risk for poor outcomes from CSCC, tumor risk stratification is particularly important in optimizing the care of these patients.

The present study demonstrated superior risk stratification according to the AJCC8 criteria relative to the criteria among patients with CLL. This is consistent with the findings of a recent study that reported improved homogeneity and monotonicity of the AJCC8 criteria relative to the AJCC7 criteria when applied to the general patient population.[15] In addition, our study found improved performance of the BWH system relative to the AJCC7 system, which is similar to the findings of previous research at other institutions.[8,9] In those studies, distinctiveness, homogeneity, and monotonicity were analyzed between the competing staging systems. Owing to the infrequency of poor outcomes in high-stage tumors in the present study, statistical analysis of those parameters could not be performed. Instead, the performance of each staging system was measured with a C-index.

In our cohort of patients with underlying CLL, tumors staged as T2 according to the AJCC7 criteria were further stratified according to the BWH system into a lower-risk T2a and higher-risk T2b category. Interestingly, the BWH system also stratified AJCC7 T1 tumors into a lower-risk T1 and higher-risk T2a category. In our cohort, there were no CSCC tumors that invaded bone at the time of T staging. Because invasion of bone is required for T3 or T4 staging according to the AJCC7 criteria, risk stratification was effectively limited to the T1 and T2 tumor categories. In contrast, the BWH system defines 4 equally weighted high-risk factors to determine T stage (tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion of ≥0.1 mm, or tumor invasion beyond fat). Invasion of bone or the presence of all 4 high-risk factors is staged as T3 under the BWH system. As a result, risk stratification of tumors in this cohort occurred among 3 BWH system tumor categories despite the absence of bone invasion (T1, T2a, and T2b). This appeared to contribute to the improved risk stratification according to the BWH criteria relative to the AJCC7 criteria.

In addition, the BWH criteria trended toward superior risk stratification relative to both the AJCC8 and UICC8 criteria. Although the AJCC8 and UICC8 criteria are very similar, the AJCC8 criteria can be applied only to tumors occurring at head or neck sites. In the absence of bone invasion, the UICC8 and AJCC8 criteria risk-stratify tumors among the T1, T2, and T3 categories largely on the basis of maximum tumor dimension (with use of 2 cm and 4 cm as thresholds). The presence of defined high-risk factors (deep invasion or perineural invasion) can also lead to T3 classification in both systems. However, previous criteria such as histologic grade and tumor location have been eliminated entirely. As a result, there is an emphasis on maximum tumor dimension in the staging criteria for the UICC8 and AJCC8 systems. Although the BWH system trended toward superior risk stratification, this study was likely underpowered to detect a statistically significant difference in performance.

Table VI. Outcomes of tumors up-staged and down-staged by using the BWH T staging system

Staging system	BWH T-stage upstaging	No. of tumors up-staged	No. of poor outcomes			BWH T-stage downstaging	No. of tumors down-staged	No. of poor outcomes		
			LR	NM	DSD			LR	NM	DSD
AJCC 7	T1 → T2a	26	2	3	1	T2 → T1	4	0	0	0
	T2 → T2b	9	2	1	2					
UICC 8	T1 → T2a	30	2	3	1	T3 → T2a	4	1	0	0
	T1 → T2b	2	0	0	0					
	T2 → T2b	2	0	0	0					
AJCC 8	T1 → T2a	9	1	2	1	T2 → T1	1	0	0	0
	T2 → T2b	3	0	0	0	T3 → T2a	6	1	0	0

AJCC7, American Joint Committee on Cancer seventh edition; *AJCC8*, American Joint Committee on Cancer eighth edition; *BWH*, Brigham and Women's Hospital; *DSD*, disease-specific death; *LR*, local recurrence; *NM*, nodal metastasis; *UICC*, Union for International Cancer Control.

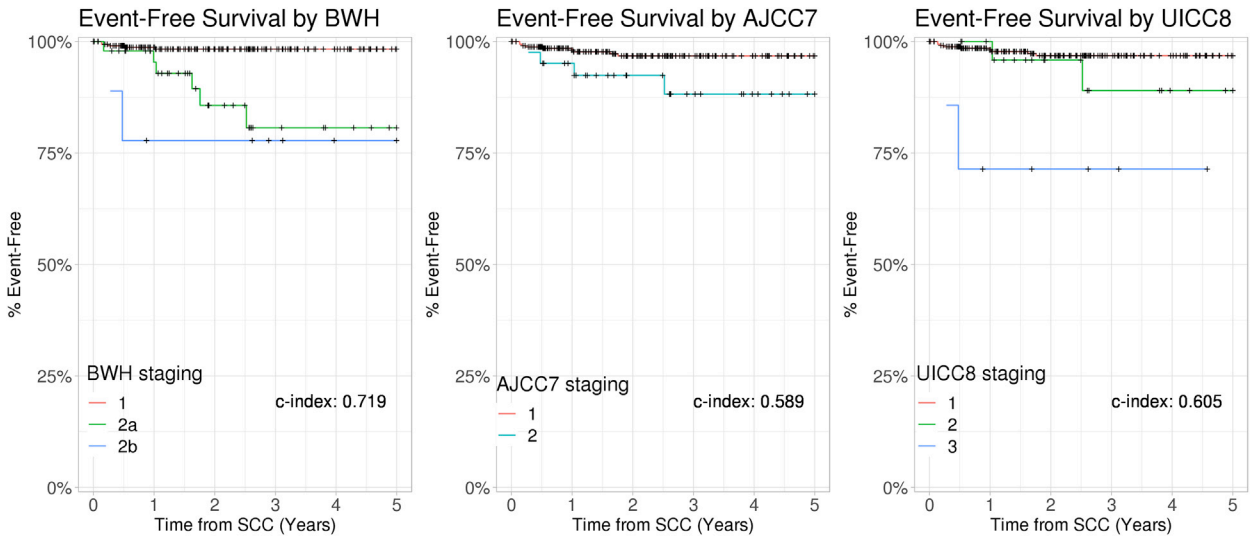

Fig 1. Event-free survival (any poor outcome) among all tumors staged according to the Brigham and Women's Hospital (BWH), American Joint Committee on Cancer seventh edition (AJCC7), and Union for International Cancer Control eighth edition (UICC8) staging systems. *SCC*, Squamous cell carcinoma.

The cumulative incidence rate of tumor recurrence was 3.0% at 3 years in the present study, which is in contrast to the 6.7% incidence rate reported in a recent population-based study authored by our research group.[5] The difference in results is due mostly to differences in demographics of the cohort (the former was based solely in Olmsted County, MN, whereas the current study was not), reduced follow-up time in the current study relative to the prior study, and inclusion criteria related to CSCC (CSCC before and after CLL diagnosis were included in the former study, whereas only CSCC after CLL diagnosis was included in the present study). We also note that the CLL treatments received by the 2 groups were not identical, which may have contributed to the observed difference in the rate of SCC recurrence.

There are several limitations to the present study, including the retrospective design and relatively small number of adverse outcomes available for statistical analysis. In addition, this study took place at an academic medical center, and the results may not necessarily be applicable to the community practice setting.

CONCLUSION

Patients with CLL are known to be at increased risk of adverse outcomes resulting from CSCC. This study has evaluated tumor staging systems for CSCC in a relatively large cohort of patients with underlying CLL. The BWH tumor staging system demonstrated superior risk stratification relative to the AJCC7 criteria, validating the results of previous research conducted at other institutions. Although

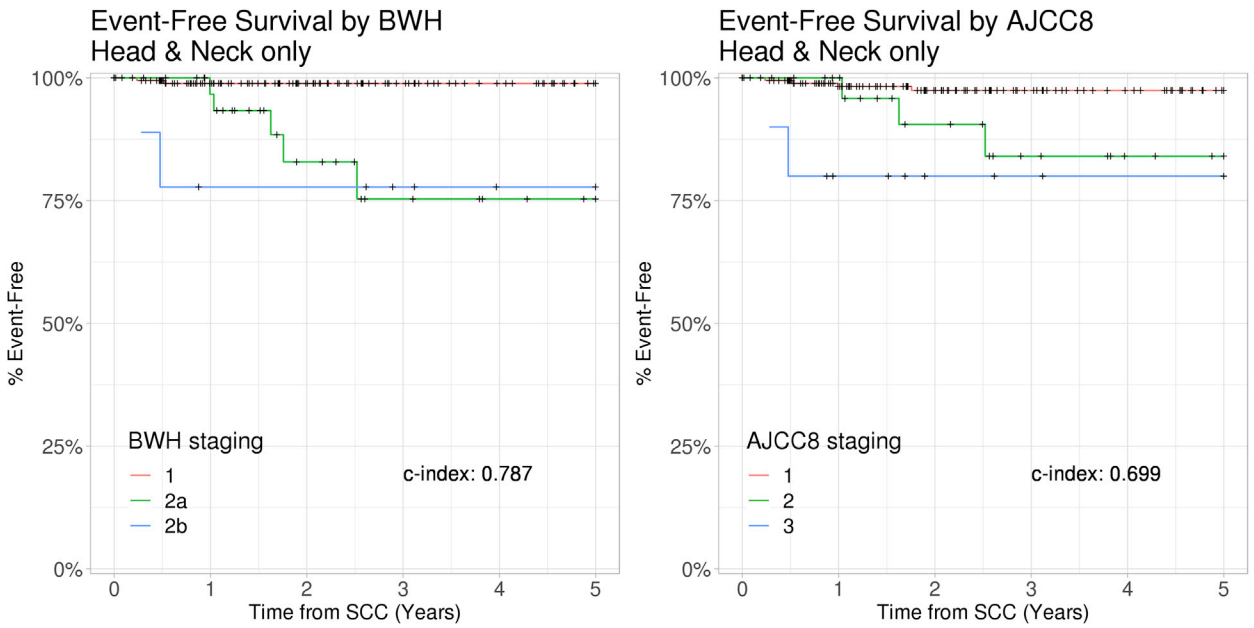

Fig 2. Event-free survival (any poor outcome) among head or neck tumors staged according to Brigham and Women's Hospital (BWH) and American Joint Committee on Cancer eighth edition (AJCC8) criteria. *SCC*, Squamous cell carcinoma.

the difference was not statistically significant, the BWH system trended toward improved performance over the AJCC8 and UICC8 criteria. Overall, the results of this study suggest that the BWH system provides significant risk stratification of CSCC tumors in patients with CLL.

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