Higher metastasis and death rates in cutaneous squamous cell carcinomas with lymphovascular invasion

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Background: Lymphovascular invasion (LVI) is an aggressive histologic finding but is excluded from current staging systems due to its lack of demonstrated independent prognostic significance.

Objective: To evaluate the impact of LVI on cutaneous squamous cell carcinoma tumor outcomes.

Methods: In total, 10,707 cutaneous squamous cell carcinoma tumors from a 20-year, retrospective, multicenter cohort were stratified by the presence (LVI^+) or absence (LVI^-) of LVI. Outcomes (local recurrence, in-transit metastasis, nodal metastasis, disease-specific death) were compared based on low (Brigham and Women's Hospital [BWH] stage T1/T2a) and high (BWH T2b/T3) tumor stages.

Results: Of the 10,707 tumors, 78 had LVI. The analysis of low-stage BWH tumors showed the LVI^+ group had a significantly higher 5-year cumulative incidence of local recurrence (LVI^+: 12.3%; LVI^-: 1.1%; $P < .01$), metastasis (LVI^+: 4.2%; LVI^-: 0.4%; $P < .01$), and disease-specific death (LVI^+: 16.2%; LVI^-: 0.4%; $P < .01$). The analysis of BWH high-stage tumors showed the LVI^+ group maintained a higher 5-year cumulative incidence of metastasis (LVI^+: 28.5%; LVI^-: 16.8%; $P = .06$) and disease-specific death (LVI^+: 25.3%; LVI^-: 13.9%; $P = .03$), however, there was no difference in local recurrence (LVI^+: 16.3%; LVI^-: 15.8%; $P = .11$).

Limitations: Retrospective study design.

Conclusion: LVI^+ cutaneous squamous cell carcinomas have higher rates of metastasis and death at 5 years. Future staging systems should consider incorporating LVI. (J Am Acad Dermatol 2022;86:766-73.)

Key words: cutaneous squamous cell carcinoma; dermatologic oncology; lymphovascular invasion; skin cancer; tumor outcomes; tumor staging.

INTRODUCTION

Cutaneous squamous cell carcinomas (CSCCs) comprise approximately 700,000 of the 3.5 million keratinocyte carcinomas diagnosed in the United States each year.[1] While most patients with CSCC have excellent prognoses with surgical clearance, a subset of CSCCs will develop poor outcomes, such as local recurrence (LR), in-transit metastasis, nodal metastasis, distant metastasis, or disease-specific death (DSD).[2,3] Several histologic and clinical factors, such as tumor diameter ≥2 cm, depth of invasion beyond fat, poor differentiation, perineural

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invasion (PNI), large-caliber nerve invasion, and recurrent disease, have been identified as risk factors for poor outcomes.[4-7] Many of these features have been incorporated into various CSCC staging systems designed to guide prognostic stratification and clinical management of tumors.[8]

Lymphovascular invasion (LVI), defined as the presence of tumor cells within an endothelial-lined lumen of a lymphatic or vascular vessel,[9] is considered to be a high-risk feature associated with metastatic disease and DSD in patients with CSCC[10-13]; however, it is excluded from staging systems because it has not demonstrated independent prognostic significance. A prospective study of head and neck CSCCs observed a 7.5-fold increase in metastasis risk if tumors had LVI.[10] Another study on excised CSCCs reported a hazard ratio for metastasis of 8.03 on univariate analysis; however, it was not statistically significant on multivariable analysis.[14] A matched-pair study comparing CSCC tumors with and without LVI showed that tumors with LVI developed poorer outcomes, but when controlling for stage, the difference between matched tumors was not statistically significant, likely due to the small sample size limiting direct statistical comparisons.[15]

Given the rarity of the finding, resulting in limited data, LVI is excluded from current CSCC staging systems. The purpose of this study is to evaluate the direct impact of LVI on CSCC tumor outcomes utilizing a multicenter cohort in order to better inform future CSCC staging systems.

CAPSULE SUMMARY

- Lymphovascular invasion is an aggressive histologic finding but is excluded from current staging systems due to its lack of demonstrated independent prognostic significance.
- Cutaneous squamous cell carcinomas with lymphovascular invasion have higher rates of metastasis and death at 5 years. Future staging systems should consider incorporating lymphovascular invasion.

METHODS

Data collection

The study was approved by the Mass General Brigham Human Research Committee and the Cleveland Clinic Institutional Review Board. Data in the present study included CSCCs from the retrospective CSCC cohorts of Brigham and Women's Hospital (BWH) and the Cleveland Clinic Foundation.[5] Data collection procedures for the BWH's CSCC cohort have been previously published.[5,16] In summary, patients diagnosed with CSCC at BWH between January 1, 2000, and December 31, 2017, were identified via the Department of Pathology's electronic database. Pathology reports were reviewed, and cases of noncutaneous SCC and *in situ* CSCC were excluded. The Cleveland Clinic Foundation's CSCC cohort was compiled using the same procedure and included patients diagnosed between March 25, 1999, and October 1, 2020. The medical records of all eligible patients were reviewed for demographic information, tumor features (including clinical diameter, anatomic depth of invasion, tumor differentiation, anatomic location, and presence of PNI or lymphovascular invasion), outcomes of interest (LR, in-transit metastasis, nodal metastasis, DSD), and the types of treatment performed, including surgical approaches and adjuvant therapies. The specimens are assessed for PNI and LVI, at two points in time: at initial biopsy and again at excision/Mohs. Pathology reports from both centers always indicate PNI or LVI when present.

Statistical analyses

Statical analyses were performed separately on BWH low-stage tumors (ie, BWH T1 and T2a) and BWH high-stage tumors (ie, BWH T2b and T3). The patient and tumor characteristics were analyzed using descriptive statistics and frequency tabulation. Cumulative incidence function curves were used to demonstrate the survival probabilities of LVI^+ compared to LVI^- tumors for competing risk end points (LR, in-transit metastasis, nodal metastasis, distant metastasis, and DSD). Death due to non-CSCC causes was considered a competing event. The follow-up time for each outcome of interest was calculated from the date of the CSCC diagnosis to the date of the outcome occurrence. For tumors that did not have any poor outcomes, the survival time was censored on the date of death or the date of last follow-up if the patient was alive at the time of data collection.

The Fine and Gray method of competing risk analysis was used to examine multivariable associations between the presence or absence of LVI and the development of outcomes of interest.[17,18] Univariate competing risk regression was used to assess factors including tumor size, depth of invasion, tumor differentiation, presence of PNI, and surgical approach. Variables with P values of $<.20$ on the univariate

Abbreviations used:

BWH: Brigham and Women's Hospital
CSCC: cutaneous squamous cell carcinoma
DSD: disease-specific death
LR: local recurrence
LVI: lymphovascular invasion
PNI: perineural invasion
SHR: subdistribution hazard ratio

analysis were included in the multivariate model. Cumulative incidence curves were adjusted for covariates included in the multivariable analysis.

All reported *P* values were 2-sided, and *P* values of <.05 were considered to be statistically significant. Statistical analyses were performed using Stata version 17.0 (StataCorp).

RESULTS

Cohort characteristics

The database search yielded 10,707 CSCCs that met inclusion criteria. The baseline cohort characteristics and outcomes of interest are summarized in Table I. The analysis of BWH T1 and T2a tumors yielded 10,063 tumors (LVI^+: 26, LVI^-: 10,037). The LVI^+ and LVI^- patients did not differ significantly in age at diagnosis, sex, smoking history, or immunosuppression. The LVI^+ group had a higher percentage of tumors with diameter ≥4 cm (LVI^+: 5/26 [19%]; LVI^-: 114/10,037 [1%]; $P < .01$), moderate or poor differentiation (LVI^+: 17/26 [66%]; LVI^-: 1261/10,037 [13%]; $P < .01$), and large-caliber nerve invasion (LVI^+: 4/26 [15%]; LVI^-: 26/10,037 [<1%]; $P < .01$). The LVI^+ group also had a higher percentage of head and neck tumors (LVI^+: 19/26 [73%]; LVI^-: 4,233/10,037 [42%]; $P < .01$), and tumors treated with standard excision (LVI^+: 13/26 [50%]; LVI^-: 3,459/10,037 [35%]; $P < .01$). LR (LVI^+: 6/26 [23%]; LVI^-: 141/10,037 [1%]; $P < .01$), metastasis (LVI^+: 4/26 [15%]; LVI^-: 72/10,037 [<1%]; $P < .01$), and DSD (LVI^+: 5/26 [19%]; LVI^-: 53/10,037 [<1%]; $P < .01$) occurred more frequently in the LVI^+ group.

The analysis of the high-stage BWH T2b and T3 tumors yielded 644 tumors (LVI^+: 52; LVI^-: 592). The LVI^+ and LVI^- patients did not differ significantly in age at diagnosis, sex, or immunosuppression. The LVI^+ group had a higher percentage of tumors with bone invasion (LVI^+: 16/52 [31%]; LVI^-: 74/592 [12%]; $P = .02$) and any PNI (LVI^+: 29/52 [56%]; LVI^-: 201/592 [34%]; $P < .01$). Patients in the LVI^+ cohort developed metastases at a greater rate (LVI^+: 13/52 [25%]; LVI^-: 86/592 [5%]; $P = .05$) and were more likely to die of CSCC (LVI^+: 13/52 [25%]; LVI^-: 79/592 [13%]; $P = .02$).

Multivariable analyses

Results of the multivariable analysis are shown in Table II. Cumulative incidence curves for BWH T1 and T2a tumors were adjusted for LVI (LR, metastasis, DSD), surgical approach (LR, metastasis, DSD), diameter ≥2 cm (LR, metastasis), depth of invasion beyond fat (LR), poor differentiation (LR, metastasis), PNI (LR, metastasis, DSD), and head and neck location (LR, metastasis). For the analysis of low-stage BWH tumors, LVI was significantly associated with LR (subdistribution hazard ratio [SHR] 12.2 [95% CI 5.1 to 29.3], $P < .01$), metastasis (SHR 9.9 [95% CI 2.9 to 34.0], $P < .01$), and DSD (SHR 41.4 [95% CI 9.1 to 188.9], $P < .01$).

Cumulative incidence curves for BWH T2b and T3 tumors were adjusted for LVI (LR, metastasis, DSD), diameter ≥2 cm (DSD), depth of invasion beyond fat (LR, metastasis, DSD), and PNI (LR, DSD). For the analysis of high-stage BWH tumors, LVI was significantly associated with DSD (SHR 2.0 [95% CI 1.1 to 3.6], $P = .03$) and trended toward significance for metastasis (SHR 1.8 [95% CI 1.0 to 3.5], $P = .06$), but there was no difference in LR (SHR 1.0 [95% CI 0.5 to 2.2], $P = .11$).

Figs 1, 2 and 3 show the cumulative incidence function curves for LR, metastasis, and DSD comparing the LVI^+ and LVI^- tumor groups. The cumulative incidence function curves for BWH T1 and T2a tumors showed the LVI^+ group had a higher 5—year cumulative incidence of LR (LVI^+: 12.3%; LVI^-: 1.1%), metastasis (LVI^+: 4.2%; LVI^-: 0.4%), and DSD (LVI^+: 16.2%; LVI^-: 0.4%) than tumors without LVI. The cumulative incidence function curves for BWH T2b and BWH T3 tumors exhibited higher 5-year cumulative incidences of metastasis (LVI^+: 28.5%; LVI^-: 16.8%) and DSD (LVI^+: 25.3%; LVI^-: 13.9%) in the LVI^+ group but comparable rates of LR (LVI^+: 16.3%; LVI^-: 15.8%) at 5 years.

DISCUSSION

To the best of our knowledge, this is the largest and first multicenter study to evaluate the impact of LVI on CSCC tumor outcomes. The results presented herein show that tumors with LVI have a higher 5-year cumulative incidence of poor outcomes, including LR, metastasis, and DSD. Interestingly, the presence of LVI in low-stage tumors had a larger effect on the development of poor outcomes, with 12, 10, and 41 times greater risks of LR, metastasis, and DSD, respectively, in LVI^+ tumors than in LVI^- tumors. Since these tumors have none or only one of the established risk factors, LVI may have a greater influence on a tumor's risk. However, even in high-stage tumors, the rates of metastasis and DSD were almost double that in tumors without LVI at 5 years.

Table I. Patient and tumor characteristics

	BWH T1 and T2a Tumors			BWH T2b and T3 Tumors		
	LVI (n = 26)	No LVI (n = 10,037)	*P**	LVI (n = 52)	No LVI (n = 592)	*P**
Cohort			.12			.01
BWH	14 (54)	6819 (68)		27 (52)	409 (69)	
CCF	12 (46)	3218 (32)		25 (48)	183 (31)	
Age at diagnosis, years (SD)†	69.6 (12.5)	72.1 (11.9)	.30	73.2 (10.4)	72.0 (13.0)	.49
Sex, n (%)			.25			.10
Male	18 (69)	5835 (58)		44 (85)	439 (74)	
Female	8 (31)	4202 (42)		8 (15)	153 (26)	
Smoking history, n (%)			.32			.01
Yes	7 (27)	3626 (36)		27 (52)	203 (34)	
No	19 (73)	6383 (64)		25 (48)	389 (66)	
Not recorded	0 (0)	28 (<1)		0 (0)	0 (0)	
Immunocompromised§, n (%)			.74			.40
Yes	7 (27)	2079 (21)		12 (23)	169 (29)	
No	19 (73)	7956 (79)		40 (77)	423 (71)	
Diameter‡, n (%)			<.01			.07
<2 cm	15 (58)	9105 (91)		10 (19)	138 (24)	
2-3.99 cm	6 (23)	818 (8)		24 (46)	320 (54)	
≥4 cm	5 (19)	114 (1)		18 (35)	120 (20)	
Not recorded	0 (0)	0 (0)		0 (0)	14 (2)	
Depth of invasion‡, n (%)			<.01			.02
Dermis/subcutaneous fat	24 (92)	9993 (99)		19 (36)	272 (46)	
Beyond subcutaneous fat	1 (4)	31 (<1)		13 (25)	164 (28)	
Bone	0 (0)	0 (0)		16 (31)	74 (12)	
Other	1 (4)	13 (<1)		4 (8)	81 (14)	
Not recorded	0 (0)	0 (0)		0 (0)	1 (<1)	
Differentiation‡, n (%)			<.01			.75
Well	5 (19)	8322 (83)		6 (12)	99 (17)	
Moderate	15 (58)	984 (10)		8 (15)	105 (18)	
Poor	2 (8)	273 (3)		37 (71)	367 (62)	
Not recorded	4 (15)	458 (4)		1 (2)	21 (3)	
PNI, n (%)			<.01			<.01
LCNI	4 (15)	26 (<1)		13 (25)	102 (17)	
Other perineural invasion‖	6 (23)	125 (1)		16 (31)	99 (17)	
None	16 (62)	9886 (99)		23 (44)	391 (66)	
BWH Stage, n (%)			<.01			<.01
T1	7 (27)	8512 (85)		-	-	
T2a	19 (73)	1525 (15)		-	-	
T2b	-	-		35 (67)	508 (86)	
T3	-	-		17 (33)	84 (14)	
AJCC8 Stage, n (%)‡			<.01			<.01
T1	2 (8)	3360 (33)		0 (0)	0 (0)	
T2	2 (8)	299 (3)		2 (3)	56 (9)	
T3	7 (27)	159 (2)		14 (27)	217 (37)	
T4a	3 (11)	25 (<1)		7 (14)	62 (10)	
T4b	2 (8)	3 (<1)		7 (14)	16 (3)	
Not recorded	10 (38)	6191 (62)		22 (42)	241 (41)	
Location‡, n (%)			<.01			.09
Head and neck	19 (73)	4233 (42)		37 (71)	430 (73)	
Trunk	1 (4)	1118 (11)		8 (15)	59 (10)	
Upper extremity	1 (4)	2383 (24)		4 (8)	43 (7)	
Lower extremity	3 (11)	2275 (23)		0 (0)	44 (7)	
Genital/perianal	2 (8)	26 (<1)		2 (4)	10 (2)	
Not recorded	0 (0)	2 (<1)		1 (2)	6 (1)	

Continued

Table I. Cont'd

	BWH T1 and T2a Tumors			BWH T2b and T3 Tumors		
	LVI (n = 26)	No LVI (n = 10,037)	P*	LVI (n = 52)	No LVI (n = 592)	P*
Treatment‡, n (%)			<.01			.24
Mohs	7 (27)	4990 (50)		13 (25)	213 (36)	
Standard excision	13 (50)	3459 (35)		32 (62)	279 (47)	
Radiation +/- chemotherapy	5 (19)	133 (1)		5 (10)	47 (8)	
Other	1 (4)	608 (6)		0 (0)	2 (3)	
Not recorded	0 (0)	847 (8)		2 (3)	51 (8)	
Adjuvant Therapy‡, n (%)			.18			.18
Chemotherapy	1 (4)	48 (<1)		1 (2)	8 (1)	
Radiation	3 (12)	65 (<1)		13 (25)	119 (20)	
Chemotherapy and radiation	2 (8)	11 (<1)		5 (10)	27 (5)	
Outcomes, n (%)						
Local recurrence	6 (23)	141 (1)	<.01	8 (15)	84 (14)	.81
Metastasis	4 (15)	72 (<1)	<.01	13 (25)	85 (14)	.04
In-transit metastasis	1 (4)	22 (<1)	.06	6 (12)	29 (5)	.04
Nodal metastasis	1 (4)	57 (<1)	.14	6 (12)	62 (10)	.81
Distant metastasis	2 (8)	18 (<1)	<.01	8 (15)	35 (6)	<.01
Disease-specific death	5 (19)	53 (<1)	<.01	13 (25)	80 (14)	.02

BWH, Brigham and Women's Hospital; *CCF*, Cleveland Clinic Foundation; *PNI*, perineural invasion; *LCNI*, large-caliber nerve invasion; *LVI*, lymphovascular invasion; *AJCC8*, American Joint Committee on Cancer 8th edition.

**P* values based on chi square unless otherwise specified.

†*P*-value based on Student *t* test.

‡*P*-value based on Fisher's exact.

§Immunocompromised includes immune deficiency, organ transplant recipient, immunosuppressive medication, prolonged steroid use, HIV, bone marrow transplant.

‖Does not include LCNI.

Table II. Results from the multivariable analysis

	BWH T1 and T2a tumors								
	Local recurrence			Metastasis (ITM, NM, DM)			Disease-specific death		
	SHR	P	95% CI	SHR	P	95% CI	SHR	P	95% CI
LVI	**12.2**	**<.01**	**5.1-29.3**	**9.9**	**<.01**	**2.9-34.0**	**41.4**	**<.01**	**9.1-188.9**
Mohs surgery	**0.5**	**<.01**	**0.3-0.8**	0.5	.05	0.3-1.0	0.7	.31	0.3-1.4
Diameter ≥2 cm	**2.4**	**<.01**	**1.4-4.1**	**4.2**	**.02**	**2.1-8.2**	(Underpowered)		
Depth of invasion beyond fat	1.2	.88	0.2-8.5	(Underpowered)			(Underpowered)		
Poor differentiation	**4.6**	**<.01**	**2.6-8.1**	**7.9**	**.02**	**3.7-16.9**	(Underpowered)		
PNI	**2.4**	**.01**	**1.2-4.6**	**2.9**	**.03**	**1.1-7.4**	**4.5**	**.04**	**1.1-18.8**
Head/neck location	**2.2**	**<.01**	**1.4-3.5**	**3.8**	**.02**	**1.9-7.6**	(Underpowered)		

	BWH T2b and T3 tumors								
	SHR	P	95% CI	SHR	P	95% CI	SHR	P	95% CI
LVI	1.0	.11	0.5-2.2	1.8	.06	1.0-3.5	**2.0**	**.03**	**1.1-3.6**
Diameter ≥2 cm	NS on univariate			NS on univariate			**2.0**	**.02**	**1.1-3.6**
Depth of invasion beyond fat	1.3	.13	0.9-1.7	1.3	.10	1.0-1.7	**1.9**	**<.01**	**1.5-2.6**
PNI	1.4	.12	0.9-2.2	NS on univariate			1.4	.11	0.9-2.3

Stastistically significant findings are in bold text.

BWH, Brigham and Women's Hospital; *ITM*, in-transit metastasis; *NM*, nodal metastasis; *DM*, distal metastasis; *SHR*, subdistribution hazard ratio; *LCNI*, large-caliber nerve invasion; *LVI*, lymphovascular invasion; *NS*, not statistically significant ($P > .20$).

Although LVI is acknowledged as a very high-risk feature for CSCC tumors in the latest edition of the National Comprehensive Cancer Network guidelines, it is excluded from current staging systems, including the American Joint Committee on Cancer 8th edition, International Union Against Cancer, and BWH tumor staging systems, due to insufficient data to prove independent prognostic significance.[16,19,20]

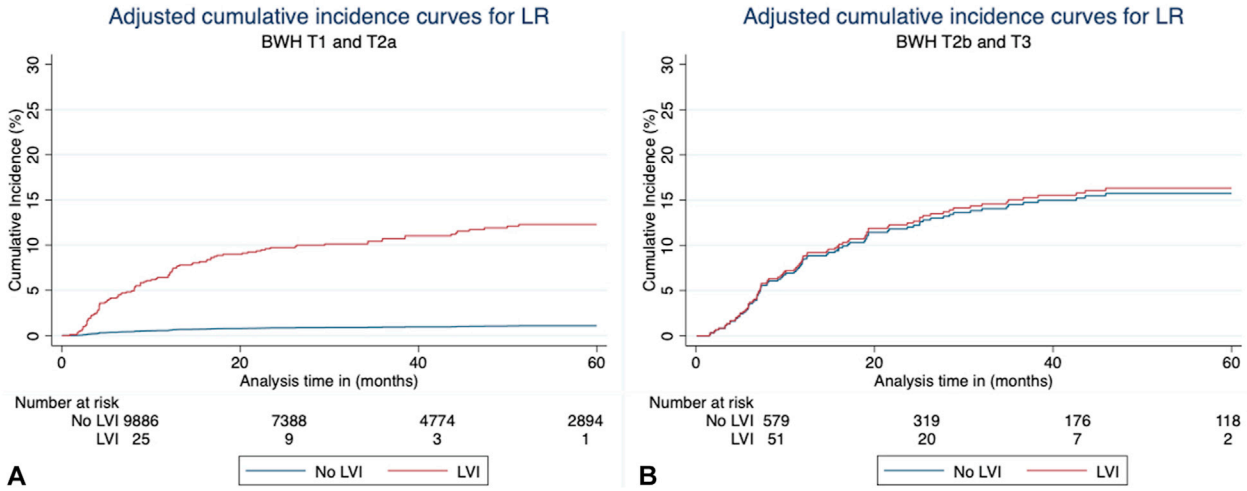

Fig 1. Adjusted cumulative incidence curves for local recurrence: (**A**) BWH T1 and T2a tumors, (**B**) BWH T2b and T3 tumors. *BWH*, Brigham and Women's Hospital; *LR*, local recurrence; *LVI*, lymphovascular invasion.

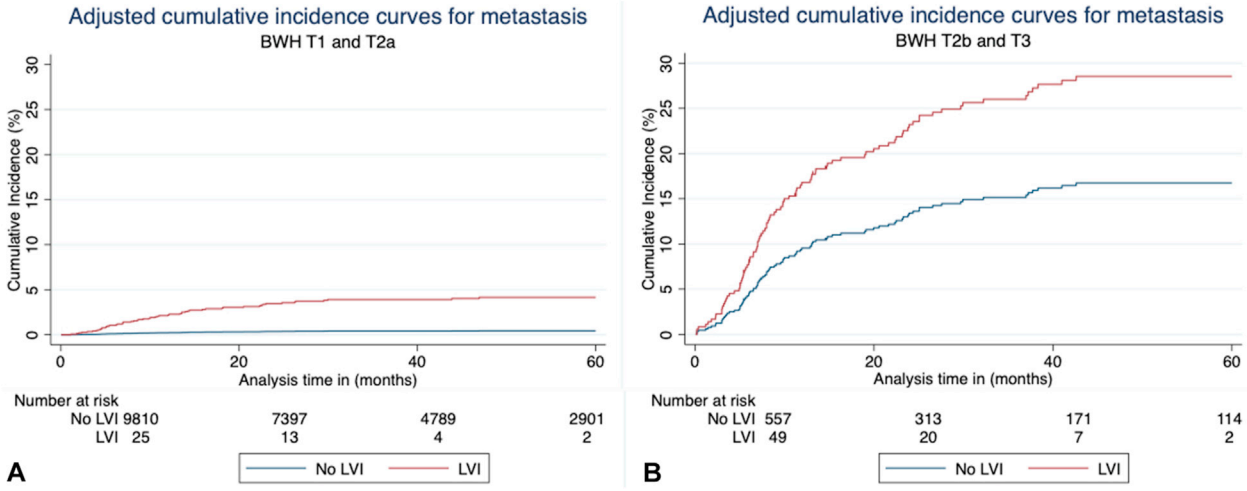

Fig 2. Adjusted cumulative incidence curves for metastasis (in-transit metastasis, nodal metastasis, distant metastasis): (**A**) BWH T1 and T2a tumors, (**B**) BWH T2b and T3 tumors. *BWH*, Brigham and Women's Hospital; *LVI*, lymphovascular invasion.

The data presented herein provide evidence that LVI does influence the development of poor outcomes in the absence of other risk factors and, thus, should be considered a high-risk factor. Tumor staging systems serve as important tools to risk stratify tumors in order to guide clinical management.[8] Cancer staging also provides a standardized lexicon so that tumors can be compared equitably across different clinical settings and providers.[21] In the case of CSCC, staging is critical in separating rare, high-risk tumors from the low-risk majority. Patients with high-risk tumors, especially those with multiple risk factors, are offered closer surveillance and considered for adjuvant therapy.[22]

Prior data has shown LVI to have a greater influence on metastasis and disease-related death than local tumor control. In cases of local or regional CSCC, the presence of LVI correlates with lymph node metastasis. A prospective study of 193 patients with head and neck CSCC found that nodal metastasis was significantly associated with LVI ($P < .0001$).[10] More recently, a study of 53 patients with high-risk CSCC treated with wide local excision and sentinel lymph node biopsy showed that LVI was associated with the presence of nodal disease (Cohen d = 3.52; 95% CI 1.83 to 5.21).[11] Another retrospective study of 93 patients with primary, ≥2-cm CSCCs of the temporal region found that a quarter

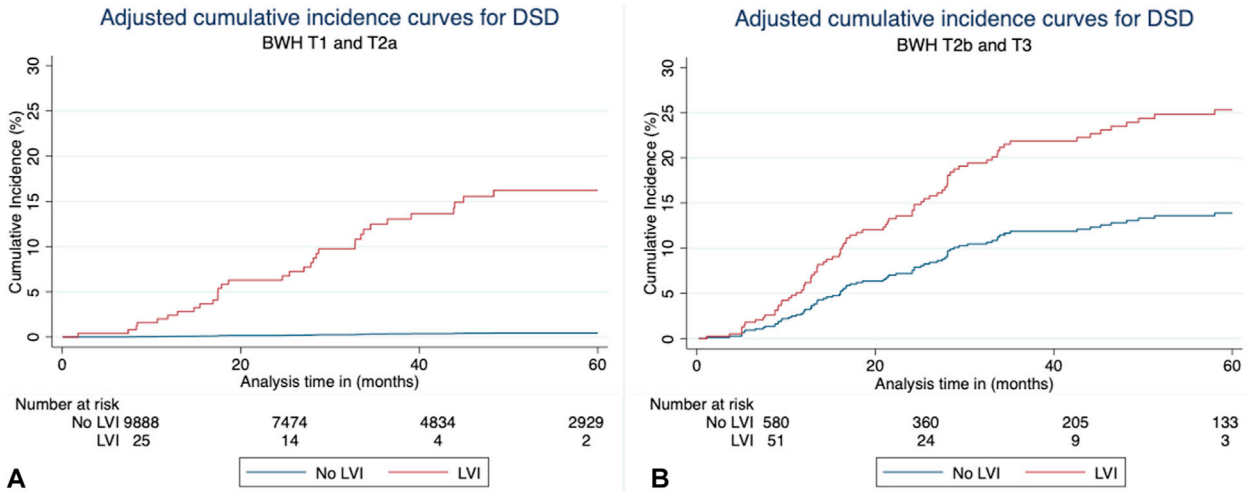

Fig 3. Adjusted cumulative incidence curves for disease-specific death: (**A**) BWH T1 and T2a tumors, (**B**) BWH T2b and T3 tumors. *BWH*, Brigham and Women's Hospital; *DSD*, disease-specific death; *LVI*, lymphovascular invasion.

of tumors had parotid involvement, and, of these, 39% had LVI ($P = .0004$).[23] The data presented herein for the high-stage tumors have similar findings, with higher rates of metastasis and death at 5 years in both high- and low-stage tumors with LVI; however, the higher rate of metastasis in high-stage tumors was not statistically significant. Interestingly, LR was also significantly lower in low-stage tumors without LVI.

This study is subject to a few limitations. The CSCC cohorts utilized in this study are from 2 academic medical centers and may not represent the population at large of patients with CSCC. These institutions may treat CSCCs differently than elsewhere, thus impacting tumor outcomes. However, the uniform reporting of risk factors should translate to similar risks for poor outcomes among tumors with similar risk profiles, regardless of the treating physician or institution. This study is also retrospective, and it is possible that LVI and other tumor risk factors were underreported.

CONCLUSION

LVI appears to independently influence LR and metastasis in low-stage CSCCs and disease-related death in all tumors. High-stage tumors with LVI showed greater rates of metastasis than high-stage tumors without LVI; however, the difference was not statistically significant. Future staging systems should consider incorporating LVI as a risk factor, but in the interim, CSCCs with LVI should be considered at high risk for metastasis and death and managed accordingly.

Conflicts of interest

Dr Koyfman has received research funds from Merck and BMS, is a consultant for Merck and Regeneron, serves on the advisory board of Castle Biosciences, and is the recipient of honoraria from UpToDate. Authors Kus, Murad, Smile, Chang, Ashrafzadeh, Zhou, Ilori, Vidimos, Schmults, and Ruiz have no conflicts of interest to declare.

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