Immunosuppression is associated with an increased risk of distant metastases in high-risk cutaneous squamous cell carcinoma: A retrospective cohort study

To the Editor: Cutaneous squamous cell carcinoma (CSCC) is the second most frequent cancer in humans, and it can be both locally invasive and metastatic to distant sites. Despite distant metastases (DM) being rare in CSCC, some patients do develop DM. Immunosuppression (IS) is a risk factor for CSCC. Several clinical practice guidelines consider IS to be a high-risk feature for recurrence in CSCC, but it is currently excluded from most popular staging systems. Some recent studies, including a meta-analysis,[1] have explored the prognostic impact of IS in CSCC.[1,2] However, there is still certain lack of knowledge on IS impact on DM as a separate outcome instead of pooling it with nodal metastases given the very small number of studies with small series in which DM was evaluated.[1]

We evaluated a cohort of patients diagnosed with CSCC between 2010 and 2019 at the University Hospital of Salamanca, Spain. CSCCs were selected when 1 or more of the following risk factors of poor prognosis were present: tumor diameter≥2 cm, thickness>6 mm, perineural invasion, poor differentiation, lymphovascular invasion (LVI), invasion beyond the subcutaneous fat, desmoplasia, tumor budding, and IS. When more than 1 CSCC was diagnosed in the same patient, that supposing the greatest risk was considered. A cohort of 781 high-risk CSCCs was retrieved (218 in immunosuppressed). In this cohort, there were 100 local recurrences, 97 nodal metastases, 30 DM, and 64 patients died from CSCC.

Table I. Characteristics of cutaneous squamous cell carcinomas developed in immunocompetent (group 1) and immunocompromised (group 2) patients and the cause of immunosuppression in these cases

	Group 1 Inmunocompetent (*N* = 563)	Group 2 Immunosuppressed (*N* = 218)	*P* value
Patient history			
Age, Me (IQR)	86 (10)	82 (12)	**.01**
Sex			
Male	280 (49.7 %)	142 (65.1 %)	**.01**
Female	283 (50.3 %)	76 (34.9 %)	
Tumor traits			
Tumor size > 4 cm			
> 2 cm	348 (61.9 %)	145 (66.5 %)	**N.S.**
[2-4) cm	175 (31.1 %)	56 (25.7 %)	
≥ 4 cm	39 (6.9 %)	17 (7.8 %)	
Tumor thickness			
Up to 6 mm	311 (55.3 %)	126 (57.8 %)	**N.S.**
≥ 6 mm	251 (44.7 %)	92 (42.2 %)	
Tumor invasion			
Beyond fat	140 (24.9 %)	60 (27.5 %)	**N.S.**
Muscle	101 (18 %)	36 (16.5 %)	
Bone	7 (3.4 %)	6 (9.7 %)	
Tumor location			
H&N High risk	185 (33 %)	76 (34.9 %)	**.008**
H&N Low risk	150 (26.7 %)	80 (36.7 %)	
Trunk and Limbs	113 (20.2 %)	29 (13.3 %)	
Hand & Feet	109 (19.5 %)	30 (13.8 %)	

Continued

Table I. Cont'd

	Group 1 Inmunocompetent ($N = 563$)	Group 2 Immunosuppressed ($N = 218$)	*P* value
Grade of differentiation			
Good	97 (17.3 %)	44 (20.3 %)	**N.S.**
Moderate	343 (61 %)	122 (56.2 %)	
Poor	122 (21.7 %)	51 (23.5 %)	
Lymphovascular invasion			
Yes	18 (3.2 %)	4 (1.8 %)	**N.S.**
No	545 (96.8 %)	214 (98.2 %)	
Perineural invasion			
No	419 (74.6 %)	172 (78.9 %)	**N.S.**
Nerve ≤ 0.1 mm	69 (12.3 %)	25 (11.5 %)	
Nerve > 0.1 mm	74 (13.2 %)	21 (9.6 %)	
Other cause	342 (88.1 %)	129 (87.8 %)	
Follow-up months, Me (IQR)	40 (58)	31.5 (40)	**.005**
Staging			
8th-AJCC			
T1-T2	256 (45.6 %)	101 (46.3 %)	**N.S.**
T3-T4	306 (54.4 %)	117 (53.7 %)	
BWH			
T1-T2a	408 (72.6 %)	164 (75.2 %)	**N.S.**
T2b-T3	154 (27.4 %)	54 (24.8 %)	

Immunosuppression type	*n* (%)
Chronic lymphocytic leukemia	30 (13.7)
Other hematological malignancies	51 (23.4)
Solid organ transplantation	14 (6.4)
Chronic immunosuppressive treatment	5 (2.3)
Poorly controlled diabetes	32 (14.7)
Chronic renal failure	22 (10.1)
Solid tumors (excluding nonmelanoma skin cancer)	49 (22.5)
Inflammatory disease	18 (8.2)
HIV	2 (0.9)

Proportions were compared using the chi-squared test (using IBM SPSS Statistics v26). Bold values of $P < .05$ were considered statistically significant.

AJCC, The American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital; *H&N*, head and neck; *HIV*, human immunodeficiency virus; *IQR*, interquartile range; *Me*, median; *NS*, not significant.

We first compared CSCCs between immunocompetent and immunosuppressed patients (Table I). Subsequently, we explored the cumulative incidence function using the Gray test, considering death from other causes as a competing risk. Multivariate models, using Fine−Gray proportional hazard regression, were derived to assess the independence of risk factors in CSCC outcomes. Specifically, we considered BWH T-stage, LVI (relevant in CSCC prognosis[3] despite not considered for staging), gender,[1,4] and IS. We found that LVI and the T-stage were consistently associated with all poor outcome events. IS was associated with distant metastases in the univariate (HR = 2.662 [95% CI = 1.303-5.439], $P = .0072$) and multivariate (HR = 3.393 [95% CI = 1.646-6.995], $P = .00093$) analyses. Gender was not associated with prognosis in this study (Table II).

IS is unanimously considered a high-risk feature in CSCC, but it needs a more homogeneous definition given that different levels and types of IS might have different effects on prognosis.[1] While recent papers failed to identify differences in prognosis between immunosuppressed and immunocompetent patients when adjusted by T-stage,[1] all metastases were pooled together rather than splitting them by type. A recent meta-analysis demonstrated IS to be a risk factor for all poor outcome events in CSCC except for DM, but only 2 studies had explored the impact of IS in DM development.[2] Few studies have focused on DM in CSCC.[5] Here, we found that IS is a patient

Table II. Univariate and multivariate Fine-Gray regression analyses to assess the degree of association of immunosuppression, along with other tumor variables, to various adverse outcomes of cutaneous squamous cell carcinoma

		Univariate model			Multivariate model		
Outcome	**Variable**	**HR**	**IC (95 %)**	***P***	**HR**	**IC (95 %)**	***P***
Local recurrence	Gender	1.256	0.8443-1.869	.26	1.155	0.7734-1.726	.48
	Immunosuppression	1.233	0.812-1.871	.33	1.239	0.8144-1.885	.32
	Lymphovascular invasion	2.419	1.196-4.892	**.014**	1.998	0.9187-4.346	.081
	BWH (T2b/T3 vs T1/T2a)	3.018	2.043-4.458	**<.0001**	2.87	1.94-4.244	**<.0001**
Nodal metastases	Gender	0.9204	0.6195-1.367	.68	0.9022	0.6004-1.356	.62
	Immunosuppression	0.9465	0.6043-1.482	.81	1.08	0.6832-1.707	.74
	Lymphovascular invasion	5.307	2.822-9.978	**<.0001**	4.833	2.926-7.982	**<.0001**
	BWH (T2b/T3 vs T1/T2a)	4.776	3.185-7.163	**<.0001**	4.282	2.859-6.415	**<.0001**
Distant metastases	Gender	0.7545	0.3696-1.54	.44	0.6738	0.3082-1.473	.32
	Immunosuppression	2.662	1.303-5.439	**.0072**	3.393	1.646-6.995	**.00093**
	Lymphovascular invasion	6.003	2.669-13.5	**<.0001**	5.808	2.349-14.36	**.00014**
	BWH (T2b/T3 vs T1/T2a)	4.229	2.04-8.767	**.00011**	3.756	1.792-7.874	**.00046**
Disease-specific death	Gender	1.34	0.7866-2.281	.28	0.6758	0.3938-1.16	.16
	Immunosuppression	1.003	0.5545-1.816	.99	1.129	0.6181-2.063	.69
	Lymphovascular invasion	5.381	2.679-10.81	**<.0001**	3.596	1.799-7.189	**.00029**
	BWH (T2b/T3 vs T1/T2a)	7.205	4.03-12.88	**<.0001**	6.692	3.76-11.91	**<.0001**

We decided to use BWH T-stage (which encompasses several high-risk features including perineural invasion ≥0.1 mm, poor degree of differentiation, invasion beyond the subcutaneous fat and tumor size ≥2 cm), lymphovascular invasion (known to be relevant in Cutaneous squamous cell carcinomaprognosis despite not being considered in staging systems), male sex (another feature recently associated with poor prognosis in cohort and population-based studies) and immunosuppression. All these tests were carried out using R (version 4.3.0). Statistically significant *P* values (<.05) are in bold.|
BWH, Brigham and Women's Hospital.

feature independently associated with a higher risk of DM, despite there was not an association when all metastases were pooled nor with nodal metastases separately. Further studies will help define IS accurately and identify its genuine prognostic impact in CSCC and if DM development exhibits specific features compared with other outcome events.

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Funding sources: Javier Cañueto is partially supported by the (Gerencia Regional de Salud de Castilla y León, grants GRS2338/A/21 and GRS2549/A/22), by the Instituto de Salud Carlos III (ISCIII), (PI18/00587 and PI21/01207), cofinanced by European Union, and by the "Programa de Intensificación of the ISCIII, grant number INT20/00074". Sponsors and funders had no influence on the design and conduct of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, and approval of the manuscript, or the decision to submit the manuscript for publication.

Patient consent: Not applicable.

IRB approval status: Not applicable.

Key words: cutaneous squamous cell carcinoma; immunosuppression; outcome measures; staging systems.

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Conflicts of interest

None disclosed.

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https://doi.org/10.1016/j.jdin.2023.11.006