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Funding sources: this study was supported by grants from the Deutsche Forschungsgemeinschaft (German Research Foundation), project ID 369799452/404458960 – TRR237, KFO 249/GU1212/1-1 and 1-2; a MEDDRIVE grant from the Medical Faculty, TU Dresden; and a Roche research award to C.G.

Conflicts of interest: the authors declare they have no conflicts of interest.

Risk factors for distant metastasis in cutaneous squamous cell carcinoma

DOI: 10.1111/bjd.21250

Dear Editor, Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 20% of skin malignancies worldwide, with metastasis rates estimated at 5% (higher in immunosuppressed patients) and 5-year disease-specific survival in excess of 90%.[1,2] The American Joint Committee on Cancer (AJCC) 8th Edition tumour–nodes–metastasis staging defines stage IV disease as invasion of axial or appendicular skeleton, perineural invasion of the skull base, nodal metastasis > 3 cm in greatest dimension, or distant metastasis. Brunner *et al*. reported decreased 5-year survival among patients diagnosed with stage IV disease due to distant metastasis (vs. nodal disease only), warranting additional risk stratification and management of distant metastatic disease.[3] Risk factors for metastasis are well characterized; they are based on patient factors, alongside tumour histological features in the AJCC and Brigham and Women's Hospital staging systems.

Standard treatment is tumour resection with a margin of ≥6 mm for high-risk disease or ≥ 10 mm for very high-risk disease, metastatic lymph node dissection and subsequent radiotherapy with consideration for adjuvant chemotherapy.[4] Characterization of risk factors for distant metastasis is necessary and recommended by the most recent British Association of Dermatologists guidelines, aiming to detect oligometastatic disease earlier, reduce tumour burden and prevent disease-specific morbidity and mortality.[5]

A 10-year retrospective single-centre cohort study was conducted at a tertiary oncology centre with multidisciplinary cSCC diagnosis, management and follow-up on site. Electronic health records of patients with a confirmed histopathological diagnosis of cSCC between the years 2010 and 2019 inclusive were reviewed. Patients with a confirmed histological or cytological diagnosis of nodal metastasis were included. Patients with an active non-cSCC malignancy, uncertain primary or primary mucosal SCC were excluded from the final analysis. Distant metastatic disease was identified via review of imaging; data were collected at the primary tumour level regarding histological characteristics and surgical treatment. Logistic regression analysis was performed across three models: model A (unadjusted), model B (adjusted for patient characteristics) and model C (adjusted for patient and treatment characteristics).

In the study period, 3455 tumours were diagnosed in 2522 patients. Of these, 116 patients developed nodal metastasis; 11 patients were excluded from the final analysis due to incomplete primary tumour data. Twenty-six patients with nodal disease developed radiologically confirmed distant metastasis. In the overall and distant metastasis cohorts, respectively, 22 of 105 (21·0%) and four of 26 (15%) patients were female. The respective mean (SD) ages at diagnosis of the primary tumour were 74·8 (12·5) and 73·1 (16·9) years, the mean times to first nodal metastasis were 0·83 (1·29) and 0·98 (1·18) years, and 26 of 105 (24·8%) and eight of 26 (31%) patients were immunosuppressed. In total, 103 of 105 patients (98·1%) with nodal disease received therapy (surgery, radiotherapy and/or chemotherapy) aimed at treating nodal disease. Eighteen of 26 patients (69%) developed distant metastases following previously adjuvantly treated isolated nodal disease surveillance, while eight of 26 (31%) had concomitant nodal and distant metastatic disease at follow-up, with subsequent confirmation of cSCC as the metastasis source.

Sites of distant metastasis included lung (21 of 26, 81%), axial skeleton (five of 26, 19%), adrenal gland (three of 26, 12%) and kidney (two of 26, 8%). Following logistic regression analysis, AJCC 8th edition high-risk cSCC features were not deemed to be significant predictors of distant metastasis development risk (Table 1). Patients whose primary tumours exhibited poor histological grade of differentiation were more likely to develop distant metastasis. The odds ratios (ORs), 95% confidence intervals (CIs) and P-values for models A, B and C, respectively, were OR 15·8 (95% CI 2·56–97·5), P = 0·003; OR 13·8 (95% CI 2·20–85·9), P = 0·005; and OR 28·9 (95% CI 2·07–403), P = 0·012. Patients with a closer peripheral margin at initial tumour excision were more likely to develop distant metastasis: OR 1·29 (95% CI 1·00–1·66), P = 0·044; OR 1·31 (95% CI 1·00–1·72), P = 0·054; and OR 1·42 (1·04–1·95), P = 0·026 in models A, B and C. The mean margins for the nodal and distant metastasis cohorts were 7·1 mm and 4·2 mm, respectively. Histological margin < 1 mm was deemed to be an independent risk factor in model C only, with wide CIs due to the small sample size: OR 109 (95% CI 1·37–8460), P = 0·036.[5]

We report that tumour differentiation and distance from the peripheral margin at initial excision influence risk of progression from nodal to distant metastasis. This may be explained by poorly differentiated tumours undergoing epithelial-to-mesenchymal transformation and acquiring cancer stem-cell-like properties, facilitating clinically undetectable in transit metastasis.[6] The dataset shows a strong association between poor differentiation and risk of distant metastasis. Effect size cannot be accurately inferred, with wide CIs due to small sample sizes; a larger dataset may allow more precise estimation. The clinical implication of this study is that where surgically feasible, re-excision of poorly differentiated tumours exhibiting very high-risk features should be undertaken to

Table 1 Multivariate logistic regression analysis of American Joint Committee on Cancer (AJCC) 8th Edition high-risk features in cutaneous squamous cell carcinoma and their effects on development of distant metastatic disease as a subset of all metastatic disease

	Model A		Model B		Model C	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Primary tumour site[a]	1·00 (0·88–1·14)	0·98	0·99 (0·81–1·19)	0·88	0·91 (0·74–1·13)	0·41
Primary tumour size[a]	1·02 (0·96–1·10)	0·56	1·02 (0·95–1·10)	0·52	1·01 (0·94–1·10)	0·75
Primary tumour size >20 mm	2·35 (0·23–23·1)	0·46	2·07 (0·18–2·36)	0·56	5·41 (0·20–144)	0·31
Primary tumour depth[a]	1·02 (0·92–1·13)	0·69	1·01 (0·91–1·13)	0·83	0·94 (0·83–1·07)	0·36
Primary tumour ESCF[a]	6·06 (0·80–45·7)	0·080	8·15 (0·82–81·1)	0·073	13·5 (0·70–260)	0·085
Primary tumour PNI[a]	1·20 (0·20–7·38)	0·84	1·33 (0·20–9·09)	0·77	1·50 (0·15–14·9)	0·73
Primary tumour LVI[a]	2·30 (0·41–13·0)	0·35	2·20 (0·30–16·3)	0·44	0·95 (0·08–11·2)	0·97
Primary tumour ulceration	1·08 (0·19–6·16)	0·93	1·06 (0·16–7·23)	0·95	0·93 (0·10–8·79)	0·95
Primary tumour poor differentiation[a]	15·8 (2·56–97·5)	0·003**	13·8 (2·20–85·9)	0·005**	28·9 (2·07–403)	0·012*
Primary tumour distance from histological deep margin	1·06 (0·89–1·27)	0·51	1·05 (0·87–1·28)	0·59	1·10 (0·89–1·35)	0·38
Primary tumour distance from histological peripheral margin	1·29 (1·00–1·66)	0·044*	1·31 (1·00–1·72)	0·054	1·42 (1·04–1·95)	0·026*
Primary tumour histological peripheral margin <1 mm	20·2 (0·60–676)	0·093	29·1 (0·73–1168)	0·073	109 (1·37–8460)	0·036*

CI, confidence interval; ESCF, extension beyond subcutaneous fat; LVI, lymphovascular invasion; OR, odds ratio; PNI, perineural invasion. Model A: unadjusted variables. Model B: adjusted for patient age, sex and immunosuppression status. Model C: adjusted for patient age, sex, immunosuppression status, type of surgery performed at initial resection and time to development of initial nodal metastasis. The proportion of missing values per variable ranged between 0% (site, size, depth) and 18·1% (ulceration). *P < 0·05, **P < 0·01. [a]High-risk primary cutaneous squamous cell carcinoma histological feature as per the AJCC 8th Edition. Overall tumour stage as a factor was not analysed due to temporal variation in staging systems during the study period.

achieve the minimal recommended margin of 10 mm.[5] We recommend enhanced surveillance of patients with confirmed nodal metastases whose initial histology demonstrated the above features, as they have specific risk factors for developing distant metastatic disease.[7]

Acknowledgments: The authors would like to thank Ms Anita Caffola, Dermatology Data Manager at St James' Hospital, Dublin, and the Department of Histopathology at St James' Hospital, Dublin, for their invaluable assistance in facilitating data collection. Open access funding provided by IReL.

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Funding sources: the work of N.S. on this project was facilitated by the Irish INE-NDTP Academic Track Internship programme. The work of C.J.F. is supported by the Laidlaw Undergraduate Leadership and Research programme at Trinity College, Dublin.

Conflicts of interest: the authors declare they have no conflicts of interest.

A.D.I. and R.B.B. are joint senior authors.

Data Availability Statement: Research data are not shared.