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Original Research

The prognostic value of sentinel lymph nodes on distant metastasis–free survival in patients with high-risk squamous cell carcinoma

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Abstract ***Background:*** Cutaneous squamous cell carcinoma (cSCC) is the second most common cutaneous cancer worldwide. Several tumour characteristics are considered to pose an elevated risk for systemic spread of carcinoma cells ('high-risk' features). Early detection of subclinical metastases could permit early treatment and improve overall survival. To detect occult metastases and evaluate risk of future distant metastases, diagnostic extirpation of the sentinel lymph node (SLNE) is routinely performed in cutaneous melanoma and can be offered in high-risk cutaneous squamous cell carcinoma (hrcSCC). However, the clinical utility of SLNE in patients with hrcSCC remains unknown.
Material and methods: An ambidirectional cohort study with prospective patient recruitment was performed. Between July 2008 and April 2017, of 139 eligible patients, SLNE was performed in 114 cases (25 patients refused). Median follow-up was 23.7 months.
Results: We analysed the characteristics of 114 patients with hrcSCC who underwent SLNE.

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Eighty-nine patients (78.1%) were men, and 25 patients (21.9%) were women (median age 72.2 years). In multivariable analyses, histopathological detection of ulceration (hazard ratio, HR 2.9 [95% confidence interval, CI 0.7–12.2]), perineural growth (HR 3.0 [95% CI 0.6–14.6]) and clinically occult SLN metastases (HR 10.7 [95% CI 1.9–60.6]) were strongly associated with future occurrence of distant metastases. A positive predictive value of 50% was noted for patients where SLN metastasis was detected to develop distant metastases. However, distant metastases also occurred in seven patients when histopathological SLN evaluation had shown no evidence of metastases.

Conclusions: Our data suggest SLNE is not a reliable diagnostic approach to evaluate the risk of future systemic carcinoma spread and development of distant metastases in patients with hrcSCC.

1. Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer after basal cell carcinoma [1]. Sun exposure, advanced age and ultraviolet radiation (UVR)-sensitive skin number are among the most prominent risk factors for cSCC [2]. The majority of patients with cSCC is cured by complete excision or local destructive therapies and has a favourable prognosis [1,3–5]. In total, cSCCs have a metastasis rate of 3–5%. The risk to metastasise is markedly elevated for undifferentiated carcinomas (33%), for a tumour depth (TD) > 4 mm (45%) and for cSCC demonstrating perineural growth (47%) [6]. In comparison with the general population, organ transplant recipients have a 65- to 250-fold increased risk of developing metastases [7–9]. According to the 7th American Joint Committee on Cancer Cancer (AJCC) staging guidelines applicable for our cohort, TD of >2 mm, Clark level ≥ 4, perineural growth, localisation on the ear or non–hair-bearing lip, poor differentiation or undifferentiated growth are considered high-risk features [10]. In the new 8th AJCC staging guidelines, high-risk features are neglected in stage T1 and T2 and include any of the following: TD > 6 mm, invasion beyond the subcutaneous fat, perineural invasion (with additional subclassification) and minor bone erosion [11]. The Brigham and Women's Hospital staging system includes tumour diameter ≥2 cm, poorly differentiated cSCC, perineural invasion ≥0.1 mm and tumour invasion beyond fat as high-risk factors [12]. As regional nodal involvement represents an important prognostic factor [13–15], early detection of subclinical nodal disease enabling timely treatment might contribute to a prolongation of overall survival [16,17]. In contrast to melanoma, where the prognostic value of extirpation of the sentinel lymph node (SLNE) is well documented and generally accepted, the value of SLNE in high-risk cutaneous squamous cell carcinomas (hrcSCCs) is highly controversial.

Therefore, we conducted an ambidirectional cohort study with prospective patient recruitment, offering SLNE to 139 patients having hrcSCC as defined by the German guidelines (vertical growth > 2 mm, localisation on the ear or lower lip, dedifferentiation and perineural infiltration). We explored the association between these risk factors and distant metastasis–free survival. In addition, diagnostic indices and predictive values of SLN status for distant metastasis–free survival were assessed.

2. Methods

2.1. Study design and patients

Patients were included based on the German guidelines for cSCC [18]. According to the German guidelines, SLNE may be offered to hrcSCC patients with elevated risk for metastases. The following features are defined as high-risk features: vertical growth > 2 mm, localisation on the ear or lower lip, dedifferentiation and perineural infiltration. Complete excision of the squamous cell carcinoma was performed in all patients. Excision margins were controlled micrographically. SLNE was offered to all patients with a TD > 4 mm. If the TD was < 4 mm, at least three of the aforementioned risk factors had to be present additionally to include patients in our study. Of those 139 patients, 25 patients opted against SLNE. Hence, between July 2008 and April 2017, 114 patients were included. None of the patients had clinical or ultrasonographic evidence of lymph node or distant metastases at the time of SLNE. As our university hospital is a specialised centre for transplantation, nearly a fourth of the patient cohort was immunosuppressed. Patients were assigned to three different groups, dependent on TD (<4.0 mm, 4.01 mm–6.00 mm, > 6.0 mm) [1].

2.2. Diagnostic and surgical procedures

SLNE and subsequent histopathological analysis is a routine procedure at the Department of Dermatology, University Hospital Essen, Germany [19]. Conventional staining is performed with haematoxylin and eosin (H&E) as well as immunohistochemical staining with antibodies to cytokeratin. The TD was determined on formalin-fixed excisional tissue. SLN status was designated positive if carcinoma cells were detected in histopathological evaluation, negative if not.

2.3. False-negative sentinel node

The SLN was considered false negative if primary recurrence developed within 12 months after SLNE in the lymph node basin from which a tumour-free SLN had been removed [19–21].

2.4. False-positive sentinel node

The SLN was considered false positive if H&E staining suggested the presence of carcinoma cells in SLNs. Following immunohistochemical staining could not confirm carcinoma cells in SLNs.

2.5. Sensitivity

Sensitivity of SLNE was calculated as (true-positive/[true-positive + false-negative]).

2.6. Statistical analysis

Descriptive statistics of clinical and histological characteristics were calculated using Microsoft Excel. To estimate the possible impact of 'high-risk' features on metastasis-free survival, we performed univariable and multivariable Cox proportional hazards regression analysis. Results were described by hazard ratio (HR), 95% confidence interval (CI) and confidence limit ratio [22]. All regression analyses were performed by SAS, version 9.4 (SAS Institute, Cary, NC, USA). For distant metastasis–free survival, time to distant metastasis is defined as the time from day of SLNE to the day when any distant metastasis (lymph node, cutaneous and visceral) was diagnosed.

2.7. Follow-up evaluation

After SLNE, patients regularly presented for follow-up examinations. Whole body examination was performed screening for epithelial or melanocytic tumours. The site of hrcSCCs and lymph node basins (inguinal, axillar and cervical) were palpated and examined ultrasonographically initially every three months for two years, then twice a year for another three years. In cases with SLN metastases or distant metastases, these examinations were performed four times a year for five years. In addition, computed tomography scans of the head, trunk and abdomen were performed twice a year for five years if any metastases were detected.

3. Results

3.1. Patients and tumour characteristics

We analysed the characteristics of 114 patients with hrcSCC who underwent SLNE in our department. In total, 89 patients (78.1%) were men and 25 patients (21.9%) women. Twenty-nine patients were immunosuppressed; 85 patients were immunocompetent. The median age at SLNE was 72.2 years (standard deviation, SD 11.3; mean 69.4 years [range 42–89]). In total, 87 hrcSCCs were located in the head/neck region and 27 hrcSCCs on the trunk. SLNE was performed in the head region (n = 69), the cervical region (n = 18), the axillar region (n = 12) and the inguinal region (n = 15). The most common locations for SLNE of the head were preauricular (n = 21) and submandibular (n = 18) (Table 1).

3.2. Characterisation of possible risk factors for distant visceral or cutaneous metastases

The mean tumour depth (TD) of hrcSCCs was 6.2 mm (SD 2.5; median 5.9 mm [range 2.8–18]). Neither a positive SLN nor distant visceral or cutaneous metastases were identified in 47 hrcSCCs displaying ulceration, 16 hrcSCCs displaying perineural growth and 14 hrcSCCs displaying dedifferentiation histopathologically. A TD > 4 mm was the only high-risk feature in 47 patients. Of those patients with a positive SLN, one patient had one and two patients had two high-risk features in addition to TD > 4 mm. Of those patients with later occurrence of distant metastases, 4 patients demonstrated one and one patient had two high-risk features in addition to TD > 4 mm. Of those patients with a negative SLN and without distant metastases, 24 patients had one, ten patients had two and one patient had four high-risk features in addition to TD > 4 mm. The remaining patients could not be fully classified because of the lack of information (e.g. histopathological features). Patients with multiple high-risk features were not found to develop distant metastases more frequently. To further evaluate whether high-risk factors increased the risk for occurrence of distant metastases, we performed univariable and multivariable analysis. We found ulceration and perineural growth to be strongly associated with occurrence of distant metastases in univariable analysis (ulceration: crude HR 3.1

Table 1
Characteristics of patients and tumour depth of cSCC with concerning location of sentinel lymph node excision.

Characteristics	All (n = 114)	Immunocompromised (n = 29)	Immunocompetent (n = 85)
Sex, n (%)			
Male	89 (78.07%)	23 (79.31%)	66 (77.65%)
Female	25 (21.93%)	6 (20.69%)	19 (22.35%)
Median age at SLNE (range) (n = 114)	72 years (42–89)	69 years (45–84)	72 years (42–89)
Mean	69.42 years	66.86 years	70.29 years
Standard deviation	11.28	10.44	11.48
Mean TD (range) n = 114	6.23 mm (2.8–18 mm)	6.08 mm (2.9–10 mm)	6.29 mm (2.8–18 mm)
Median	5.85 mm	6.00 mm	5.8 mm
Standard deviation	2.5	1.91	2.68
SLNE localisation n = 114 >			
Head (including)	69	21	48
Mandibular angle	2	–	2
Submandibular	18	6	12
Midjugular	9	3	6
Supraclavicular	2	1	1
Occipital	1	1	–
Submental	1	–	1
Preauricular	21	6	15
Retroauricular	8	1	7
Parotid gland	7	3	4
Cervical region	18	5	13
Axillar region	12	1	11
Inguinal region	15	2	13

TD, tumour depth; cSCC, cutaneous squamous cell carcinoma.

[95% CI 0.8–12.5], perineural infiltration: crude HR 3.8 [95% CI 1.0–15.5]). In addition, a positive SLN was associated with an increased rate of distant metastasis (crude HR 10.1, 95% CI 2.0–51.1). Multivariable analysis revealed similar results after adjustment for covariates (Tables 2 and 3).

Table 2
Association between risk factors and distant metastasis free survival among 114 patients with high-risk squamous cell carcinoma.

Risk factor	N	%	5-year survival (%)	HR	95% CI
Mean TD (mm)					
≤ 6	68	60	90	Ref.	
>6	46	40	87	1.1	0.3–4.2
Perz 1 mm increment				1.0	0.8–1.3
Localisation					
Other	98	86	87	Ref.	
Ear or lips	16	14	100	n.a.	
Ulceration					
No	67	59	93	Ref.	
Yes	47	41	82	3.1	0.8–12.5
Perineural growth					
No	98	86	92	Ref.	
Yes	16	14	68	3.8	1.0–15.5
Immunosuppression					
No	85	75	88	Ref.	
Yes	29	25	92	0.8	0.2–4.0
Sentinel lymph node status					
Negative	110	96	91	Ref.	
Positive	4	4	0	10.1	2.0–51.1

Ref. indicates reference group
HR, hazards ratio; CI, confidence interval; n.a., not applicable

3.3. Clinical utility of SLNE to estimate future occurrence of distant metastases

In 52 patients with a TD between 4.01 mm and 6.00 mm, no positive SLN was detected but 4 patients developed distant metastases during the follow-up. The rate of distant metastases is 7.7% for this range of TD (4/52 patients). In 51 patients with a TD of more than 6.00 mm, 3 patients had a positive SLN (Table 4). Two of these patients (66%) also developed distant metastases. In total, 4 patients with hrcSCC TD > 6 mm developed distant metastases (4/51 = 7.84%). In our study, 9 patients developed distant metastases (9/114 = 7.89%). However, only 2 of these patients had a positive SLN. The calculated positive predictive value of patients with a positive SLN to develop distant metastases is 50% (95% CI: 7%–93%). Although the possibility to develop distant metastases after a positive SLN

Table 3
Multivariable Cox proportional hazards regression to estimate the association between risk factors and distant metastasis free survival.

Risk factor	Scaling	HR	95% CI	Confidence limit ratio
TD (mm)	Continuous	0.9	0.7–1.3	
Ulceration	0–1	2.9	0.7–12.2	17.4
Perineural infiltration	0–1	3.0	0.6–14.6	24.3
Immunosuppression	0–1	0.7	0.1–3.9	39
Positive SLN	0–1	10.7	1.9–60.6	31.9

HR, hazards ratio; CI, confidence interval; SLN, sentinel lymph node; TD, tumour depth.

Table 4
Characteristics of all 11 patients with size and location of their cSCCs who developed metastases in SLN (SLN(+)) and distant metastases.

Identification number	Sex	Age at first diagnosed (fd) cSCC (years)	Immune status (transplantation [tx])	TD (in mm)	Location of hrcSCC	Metastasis detected in SLN	Time to distant metastases (dm) after SLN (months)	Results of LND	Location of metastases	Follow-up after SLN (months)	Time to death after SLN (months)
1	m	64	Stem cell tx	6.1	Cheek	+	–	Neck dissection 4+/28 lymph nodes, tumour penetration of lymph node capsule	–	9 (uo)	–
2	m	78	Heart tx	3.1	Nose	+	–	Neck dissection 0+/11 lymph nodes	–	7 (uo)	–
3	w	75	–	6.1	Capillitium	+	26	Neck dissection 0+/9 lymph nodes and parotidectomy	Cutaneous	52*	–
4	m	63	–	10.0	Back	+	5	LND axilla 2+/8 lymph nodes, tumour penetration of lymph node capsule	Lung	18	18
5	m	61	Liver tx	4.6	Capillitium	–	3	–	Cutaneous	9	9
6	m	69	Heart tx	2.9	Capillitium	–	2	–	Lung, cutaneous	–	6
7	m	86	–	9	Forehead	–	28	–	Cutaneous	28	–
8	m	42	–	5.0	Foot	–	16	–	Cutaneous, LN popliteal	19	19 (S)
9	w	77	–	7.2	Capillitium	–	2	–	Parotid gland (ipsilateral)	12*	–
10	m	78	–	4.9	Hand	–	6	–	Lung	6	–
11	m	77	–	6.0	Lower lip	–	9	–	Lung, cutaneous	43	43

Depicted are patients with SLN (+) and no distant metastases, patients with SLN (+) and distant metastases and patients with SLN (–) and distant metastases.
*Wanted to continue follow-up observation close to their home.
TD, tumour depth; uo, under observation; S, suicide; SLN, sentinel lymph node; hrcSCC, high-risk cutaneous squamous cell carcinoma; LND, lymph node dissection; m, man; w, woman.

is increased to 14 folds (odds ratio = 14.71 [95% CI 2.5–186.4]), the reliability of a negative SLN to predict distant metastasis–free survival is limited. Seven patients had a negative SLN and developed distant metastases during follow-up (Table 4).

3.4. False-negative and false-positive SLNs and sensitivity

In our cohort study, no false-negative and no false-positive SLN could be determined. As we determined 4 patients with histopathologically confirmed SLN metastases, we calculated a sensitivity of 100% for SLNE.

3.5. Follow-up and distant metastasis-free survival

The patients were followed up for a median duration of 23.7 months (mean 30.4 months, 105 months at maximum). Kaplan–Meier graphs contain patients with a positive SLN and those with a negative SLN. The distant metastasis–free survival probability during follow-up significantly decreases if metastases were detected in SLNs (Multiple-adjusted HRs for immunosuppression, mean tumour diameter, localisation of hrcSCC on the head–neck region, histological perineural infiltration and histological ulceration: HR = 9.1 [95% CI 1.4–57.8]) (Fig. 1). Thirty-two patients (28.07%) died during follow-up; of which, 4 patients died related to hrcSCC after distant metastases (4/32 = 12.5%).

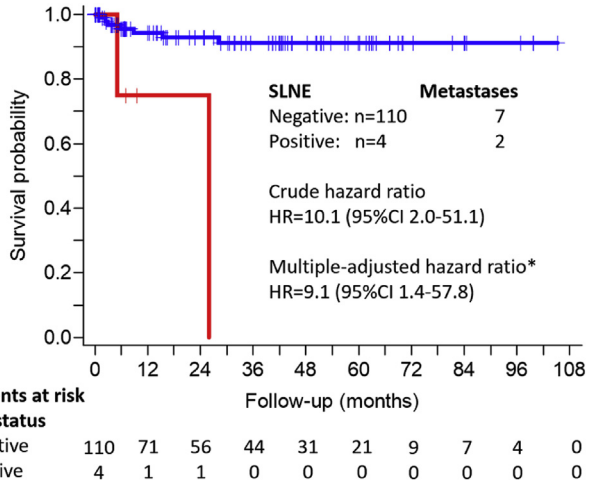

Fig. 1. Kaplan–Meier curve with the distant metastasis–free survival probability for patients with (positive) and without (negative) metastases in SLN over 108 months (blue line: SLN negative, red line: SLN positive, *adjusted for immunosuppression, histopathological ulceration in primary hrcSCC, histopathological perineural infiltration in primary hrcSCC, localisation of primary hrcSCC on the ear or perioral and tumour depth). SLN, sentinel lymph node; hrcSCC, high-risk cutaneous squamous cell carcinoma; SLNE, extirpation of the sentinel lymph node; CI, confidence interval.

4. Discussion

To the best of our knowledge, this is the largest study ever performed to evaluate the clinical utility of SLNE for patients with hrcSCC. In univariable and multivariable analyses, perineural growth and ulceration in primary hrcSCC were found to be associated with future occurrence of distant metastases, in line with previous observation [6,18]. Although we could not detect an elevated HR for TD being associated with distant metastases when we dichotomised TD (≤6 mm and >6 mm), we still determined a HR of 2.0 (95% CI 0.4–9.8) when the cut-off was set at 8 mm (Table 2). In our cohort, 4 patients (3.5%) showed a positive SLN. In contrast, the overall reported frequency of a positive SLN is 11.3%–29.4% [23–28]. Owing to the vast heterogeneity of defining hrcSCC and offering SLNE, the inclusion criteria of those reported studies have varied greatly and will affect the reported risk of SLN metastases. In our cohort, patients with hrcSCCs located on the head and neck region represented 75% and immunecompromised 25%. In those publications mainly referring to head and neck hrcSCCs, the investigators' calculations are commonly based on multiple summarised retrospective studies. Such studies lack independent and external validation resulting in the risk of mis-scoring. In addition, publication bias tends to account for divergence and might contribute to an artificially elevated rate of a positive SLN.

One patient in our study was classified SLN positive as micrometastases were detected. In the following complete lymph node dissection (LND), no additional lymph node metastases could be determined. After follow-up observation of 7 months (Table 4, P2), no distant metastases occurred. As previously described for breast cancer and melanoma, micrometastasis confined to the SLN may not spread systemically and therefore have no impact on overall survival [29]. Should this phenomenon apply to hrcSCC, complete lymphadenectomy, currently performed in affected patients, is probably unnecessary. Still, the limited follow-up time for this patient needs to be considered as well. In our study, 2 of 4 positive SLN patients developed distant metastases (Table 4). Those patients both underwent LND and adjuvant radiation therapy. For detailed results of the LND, please refer to Table 4.

In our study, the positive predictive value for a patient with a positive SLN to develop distant metastases is 50%. To fully evaluate clinical value of SLNE in hrcSCC, patients with distant metastases after negative SLN need to be provided as well. Our rate for occurrence of distant metastases, despite a former negative SLN (7/110 = 6.3%), underlines the reported frequency of 10–33% [14,30,31]. Development of distant metastases, despite a negative SLN status, indicates an additional pattern of metastases of hrcSCCs beside

lymphatic cell spread. This result questions the value of SLNE in hrcSCC.

According to Marks *et al.*, metastases of SCC might increase up to 24 months after primary diagnosis [32]. Existing literature has a number of limitations, including small patient cohorts and short median follow-up periods (generally < 20 months) [16,25–27,33]. In our cohort, two patients with a negative SLN developed metastases more than 24 months after SLNE. It would, therefore, appear mandatory that follow-up is available for at least 24 months to concisely evaluate clinical utility of SLNE in hrcSCC.

In melanoma, larger studies have shown that SLNE does not prolong overall survival [34] neither does nodal basin dissection after positive SLN [35]. To our knowledge, there are no randomised controlled trials that have analysed whether SLNE may improve the prognosis of cSCC.

As SLNE is an invasive surgery with side effects, we question if the limited clinical utility to predict future occurrence of metastases observed in our study justifies the risks and costs of SLNE in hrcSCC. Health-care costs for SLNE have been calculated between $10096 to $15223, compared with $1000 and $1740 for wide excision. Considering the low prevalence rate in our study, the costs of identifying a single positive SLN is between $287736 and $434140 [36]. Hence, ultrasonographic screening examinations are suggested to be the most suitable tool for identifying relevant structural changes induced by lymph node metastases during follow-up. Performing serial ultrasound nodal screening in the follow-up period after primary tumour resection instead of SLNE has been debated [37,38].

Several possibilities exist why SLNE is presumably not an accurate diagnostic intervention to evaluate future occurrence of distant metastases. The majority of hrcSCCs are located on the head and neck region with common bilateral drainage in this anatomic region [39].

In human skin, adjacent cells are held together by adhesion molecules such as E-cadherin. Single cell invasion occurs when the tumour cells no longer express adhesion molecules during the epithelial–mesenchymal transition and subsequently move more freely in the tissue. In the collective invasion of the cSCC, on the other hand, the tumour cells maintain contact with their neighbouring cells by expression of adhesion molecules. At the same time, the expression of podoplanin in cSCC increases the motility of the tumour cells even if, at the same time, E-cadherin secures the connection to the neighbouring cells [40,41]. Thus, in case of collective invasion of cSCC, a tumour invasion front is created, which can move into the surrounding tissue as well as into tumour-near lymphatic vessels. The tumour cell invasion front, which dissolves from the primary, may have a size of> 120 μm and obstruct afferent lymphatic vessels. Thus, tumour invasion behaviour of cSCC by lymphatic vessel obstruction would explain the high rate of cutaneous metastases in our results. Five of 9 patients with distant metastases displayed cutaneous metastases after a negative SLN.

4.1. Limitations

Although we present the largest cohort study of hrcSCC to date, the study size is still too small to provide precise estimates of diagnostic indices and hazard ratios.

5. Conclusion

Clinical utility of SLNE in hrcSCC using high-risk criteria is limited, as outlined previously. In our cohort, negative SLN is not a reliable procedure to exclude occurrence of distant metastases in patients with hrcSCCs. Novel diagnostic approaches for patients with hrcSCC should be evaluated.

Author contributions

J.K. and I.S. had full access to all the data in the study, took responsibility for the integrity of the data and the accuracy of the data analysis, contributed in study concept and design and carried out study supervision. Acquisition, analysis and interpretation of data were carried out by all the authors. Drafting of the manuscript was carried out by P.J., A.S., I.S. and J.K. The manuscript was critically revised for important intellectual content by all the authors. Statistical analysis was carried out by P.J., A.S., I.S. and J.K. P.J., S.M., T.B. and D.S. contributed in administrative, technical or material support.

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Conflict of interest statement

D.S. reported receiving consultancy fees, having board membership and receiving lecture fees from GlaxoSmithKline, Novartis, Amgen, Bristol-Myers Squibb, Roche, Genentech, Boehringer Ingelheim and MSD. The other authors declare no competing financial interests.

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Appendix A. Supplementary data

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