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INVESTIGATIVE REPORT

Clinical and Histological Prognostic Factors for Local Recurrence and Metastasis of Cutaneous Squamous Cell Carcinoma: Analysis of a Defined Population

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Cutaneous squamous cell carcinomas (cSCC) can recur locally and can metastasize. The objective of this study was to identify clinical and histopathological prognostic factors for local recurrence and metastasis in cSCCs at any body site. Clinical and histopathological data were collected from 224 patients with cSCC. During the median follow-up period of 43 months (range 0–73 months) the cumulative probabilities of recurrence-free survival at 1, 2 and 4 years post-treatment were 98.0%, 96.9% and 94.7%, respectively, and for metastasis-free survival 98.1%, 97.0% and 95.9%, respectively. In univariate survival analyses, significant predictors for local recurrence were tumour diameter and tumour thickness. For metastasis this was invasion of deeper structures, location on the ear, poor differentiation, tumour diameter and tumour thickness. In multivariate survival analysis, every millimetre increase in both tumour diameter and tumour thickness were independent predictors for local recurrence as well as for metastasis and, therefore, it is important to report these in patients' files. Defining prognostic variables is important for diagnostic work-up, treatment and follow-up for an individual patient. ***Key words: skin cancer; risk factors.***

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Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers of the skin. It has an annual incidence of 16 per 100,000 patients in Northern Europe and 754 per 100,000 patients in Australia, with the highest occurrence among elderly men (1). Worldwide incidence has increased rapidly in recent decades, and studies predicting a marked increase in cSCC over the next decade are of great concern to dermatologists and other physicians treating cSCC (2–4). The majority (80–90%) of cSCC have their origin on the skin of the head and neck region, due to years of chronic ultraviolet sun exposure mainly as a result of an outdoor occupation (5, 6). Although most people will not die of cSCC, there is a subgroup of these tumours that has metastatic spreading ability with fatal consequences (7). Metastasis occurs in 4–5% and local recurrence in 3–8% (8–13). It is of great importance to define prognostic factors in order to estimate the risk of metastasis and local recurrence of a single tumour because of the implications for diagnosis, treatment and follow-up.

Features such as perineural invasion, immunosuppression and poor differentiation are known predictors of higher risk for metastasis and local recurrence (13–16). An increasing number of studies have emphasized the potential of tumour thickness as a prognostic factor for metastasis and local recurrence (11, 17–19). The Union for International Cancer Control (UICC) has adjusted the tumour-node-metastasis (TNM) staging system in 2009 and included prognostic factors (20). In contrast to the earlier staging system, tumours classified as T3 are now those tumours invading extradermal structures, such as bone, cartilage or skeletal muscle. Tumours invading the skull-base or axial skeleton are classified as T4.

The aim of this study was to determine which clinical and histopathological features of cSCC are associated with an increased risk of metastasis and local recurrence in cSCCs distributed over the whole body.

MATERIALS AND METHODS

Patients and procedures

The Comprehensive Cancer Centre the Netherlands (CCCNL), a regional registry, provided the data from all patients diagnosed with a cSCC between 1 January 2005 and 31 December 2007 at Maastricht University Medical Centrum (MUMC). MUMC is both a regional hospital and a reference centre for dermatological oncology in The Netherlands. Patients were treated with a curative intent. Inclusion criteria were patients with histopathologically confirmed cSCC at any body site. Excluded were patients with cSCC *in situ* (e.g. Bowen's disease, actinic keratosis and erythroplasia of Queyrat).

One tumour per patient was used for analysis. In patients who developed more than one cSCC during the study period, only

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the first diagnosed cSCC with corresponding histopathological findings was taken into account. Patient age was defined as the age at the moment of histopathological diagnosis.

Patient-related data, such as date of birth, gender, history and number of previous cSCC, immune suppression state, exposure to ionizing radiation and presence of genodermatosis, were extracted from electronic and hard copy patient files, as were tumour-related factors, such as localization, tumour diameter, and data on therapy, local recurrence or metastasis of the present cSCC and survival status. Skin biopsies and surgical (re-)excisions were examined microscopically and the diagnosis of cSCC was confirmed histopathologically by dermatopathologists. Histopathological slides were evaluated retrospectively by 2 independent investigators, a third-year pathology resident and a sixth-year medical student, who both evaluated all slides. The last-mentioned attended an intensive course, given by a dermatopathologist, in evaluating histological sections of cSCC. Consensus was achieved in case both investigators recorded different results. A random selection of histopathological slides (22%) was evaluated by a dermatopathologist.

The following data were recorded: type of cSCC, tumour thickness and stage according to the 2009 UICC TNM classification. The following histopathological features were assessed; degree of differentiation, presence or absence of desmoplasia, perineural invasion, angio-invasion, inflammatory cell response, ulceration, necrosis, infiltrative growth, proliferation, actinic keratosis around cSCC, endo- or exophytic growth. Epidermal and deep resection margins, in mm, were measured exactly. Tumour thickness and macroscopic diameter were measured with an accuracy of 0.1 and 1 mm, respectively. Tumour thickness was measured starting at the stratum granulosum. Tumours were grouped into stages I–IV at the time of treatment. Differentiation was graded on a scale of good, moderate or poor (21). Inflammation response was recorded, with presence of lymphocytes, plasma cells, eosinophils, neutrophils and histiocytes. Tissue was obtained from the Maastricht Pathology Tissue Collection (MPTC). Collection, storage and use of tissue and patient data were performed in agreement with the "Code for Proper Secondary Use of Human Tissue in the Netherlands" (22).

Surgical excision was performed with a standard clinical safety margin of 5 mm. In case of high-risk tumours in the head and neck region, larger margins up to 10 mm were used. The following histopathological features were assessed: degree of differentiation, presence or absence of desmoplasia, perineural invasion, angio-invasion, inflammatory cell response, ulceration, necrosis, infiltrative growth, proliferation, actinic keratosis around cSCC, endo- or exophytic growth. Re-excision was performed if excision borders still contained tumour cells or if tumour cells were close to the resection border. In a few cases of tumours in cosmetically sensitive areas, Mohs surgery was performed as described previously (23). When the resection margins were tumour-free on frozen section an additional safety margin of 2 mm was taken. In cases where no excision was performed, the biopsy was used for evaluation of all the mentioned variables.

Patient follow-up was performed every 3 months in the first year, every 4 months in the second year, and every 6 months during the following 3 years, until 5 years after diagnosis. Transplant patients and tumours with a diameter >20 mm were seen more frequently (24, 25). When lymph node or distant metastasis was suspected in T2 cSCC of the head/neck, an ultrasonic guided biopsy was performed. If local recurrence was suspected, a biopsy was performed for histopathological confirmation. Tumour residue was defined as tumour tissue that was present after incomplete surgical excision within 3 months post-treatment. Local recurrence was defined as a cSCC that was diagnosed after radical treatment or after more than 3 months in case of incomplete excision. Both residual and recurrent tumour tissue were defined as tumour tissue within 0.5 mm of the treated area. Discovered metastases or local recurrences were documented carefully, including the number of metastases, location and time to this event. In patients with metastasis and a history of multiple cSCCs, the tumour from which the metastatic disease came was determined by the tumour closest to the first draining lymph node. The time to metastasis or local recurrence was defined as the time from the date of treatment (excision or re-excision) to the date a metastasis or a recurrence was diagnosed. Study follow-up was closed on 31 August 2011.

Statistical analysis

Inter-observer agreement was evaluated by Cohen's kappa coefficient and the intraclass correlation coefficient (ICC) (26). The effect of clinical and histopathological features of cSCC, evaluated by the first 2 observers, on local recurrence and metastasis was evaluated using univariate and multivariate Cox proportional hazard models. Recurrence-free survival was defined as the absence of any local recurrence or metastasis during follow-up. Follow-up time was calculated from the date of treatment to the date of recurrence or the date of last follow-up (censoring date). Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. p-values ≤ 0.05 were considered to indicate statistical significance. All data analyses were performed with SPSS–PC version 18.0 (SPSS, Chicago, IL, USA) and STATA version 11 (STATA Corp., Texas, USA).

RESULTS

Descriptiones of study population

In the study period from 1 January 2005 to 31 December 2007, 224 patients were diagnosed with a cSCC. The population comprised 131 males (58.5%) and 93 females (41.5%), mean age 72 years (range 12–91 years). All patient characteristics are summarized in Table I. A total of 35 patients (15.6%) were immunosuppressed; 22 patients with organ transplants, 6 with leukaemia, 4 with non-Hodgkin's lymphoma and 3 using immunosuppressive medication. Median follow-up was 43 months (range 0–73 months).

Mean clinical tumour diameter was 13.3 mm (median 10.0; range 2.5–60.0) with 83.5% categorized into ≤20 mm. The most frequent primary site was the head and neck region (excluding ear and lip) in 51.3% ($n=115$). Seventy-six percent ($n=171$) of patients were categorized into stage I of the American Joint Committee on Cancer (AJCC) staging system 2009 at time of diagnosis.

Surgery was part of the treatment in 91.1% of patients. Mohs surgery was performed in 3 patients. The most common indication for radiotherapy (RT) was as adjuvant treatment in case of positive or narrow resection borders. One ear, one hand digit and one leg were amputated. Four patients did not receive any treatment. One patient had a biopsy-proven cSCC on his hand, but 2 weeks after the biopsy there was no visible lesion and no further treatment was performed. Another patient with metastasis received no therapy because he died within 2 weeks after diagnosis. One patient with cSCC extension into the orbita, sinus and nervus subra-orbitalis was inoperable and incurable. The fourth patient received no therapy, but the reason was not known.

Table I. *Characteristics of the study population*

Characteristics	No disease progression ($n=207$)	Local recurrence ($n=11$)	Metastasis ($n=7$)
Age, years			
Mean, range	71.8 (12–91)	74.9 (65–88)	77.7 (71–84)
Standard deviation	12.1	8.5	4.2
Median	75.0	73.0	78.0
Gender, *n* (%)			
Male	119 (57.5)	6 (54.5)	6 (85.7)
Female	88 (42.5)	5 (45.5)	1 (14.3)
Time to last follow-up or event, months			
Mean, range	40.0 (0–73)	20.5 (3–53)	13.0 (0–47)
Median	43.0	12.0	2.0
Number of cutaneous squamous cell carcinoma (cSCC) in history			
0	173 (83.6)	9 (81.8)	7 (100.0)
1	19 (9.2)	1 (9.1)	0 (0.0)
≥2	7 (3.4)	1 (9.1)	0 (0.0)
Location of cSCC, *n* (%)			
Ear	19 (9.2)	3 (27.3)	5 (71.4)
Lip	12 (5.8)	1 (9.1)	0 (0.0)
Other head/neck	109 (52.7)	5 (45.5)	1 (14.3)
Trunk	16 (7.7)	0 (0.0)	0 (0.0)
Upper extremities	32 (15.5)	1 (9.1)	0 (0.0)
Lower extremities	18 (8.7)	1 (9.1)	1 (14.3)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)
Clinical tumour diameter, mm			
Mean, range	12.9 (2.5–60.0)	18.7 (8.0–51.0)	23.0 (12–35)
Tumour-node-metastasis stage, *n* (%)			
I	166 (80.2)	8 (72.7)	3 (42.9)
II	30 (14.5)	3 (27.3)	4 (57.1)
III	11 (5.3)	0 (0.0)	0 (0.0)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppression, *n* (%)			
Yes	33 (15.9)	1 (9.1)	1 (14.3)
No	174 (84.1)	10 (90.9)	6 (85.7)
Therapy, *n* (%)			
Surgical excision	192 (92.8)	8 (64.7)	5 (71.4)
Mohs micrographic surgery	3 (1.4)	0 (0.0)	0 (0.0)
Radiotherapy (RT)	3 (1.4)	1 (9.1)	1 (14.3)
Surgical excision + RT	6 (2.9)	2 (18.2)	0 (0.0)
No therapy	3 (1.4)	0 (0.0)	1 (14.3)
Death, *n* (%)	62 (30.0)	5 (45.5)	3 (42.9)
Died of cSCC	0 (0.0)	2 (40.0)	3 (100.0)
Died of other reasons	62 (100.0)	3 (60.0)	0 (0.0)

Mean tumour thickness was 3.5 mm (median 2.9; range 0.4–18.5 mm) of which 155 (69.2%) were ≤4 mm (all histopathological characteristics are summarized in Table SI; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1501). Sixteen (7.1%) tumours invaded deeper structures and moderate differentiation was most common ($n=147$, 65.6%). Perineural invasion and angio-invasion were seen in, respectively, 20 (8.9%) and 2 (0.9%) tumours.

Of all histopathological slides 22% were evaluated by a third observer (the dermatopathologist). Interobserver agreement was moderate to high for the following factors: tumour thickness ICC 0.91 (95% CI: 0.84–0.95), tumour differentiation kappa 0.65 (95% CI: 0.45–0.79) and perineural invasion kappa 0.64 (95% CI: 0.44–0.78).

Local recurrence occurred in 11 patients and metastasis in 7 patients, with a median time after treatment of 12 months (range 3–53 months) and 2 months (range 0–47 months), respectively (Table I). Clinical and histopathological characteristics of these cSCCs with local recurrence or metastasis are summarized in Table SII (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1501) and Fig. 1. One patient developed both a local recurrence and metastasis during follow-up.

Prognosis of cutaneous squamous cell carcinoma

One-, 2- and 4-year cumulative probabilities of local recurrence-free survival were 98.0% (95% CI 94.8–99.3%), 96.9% (95% CI 93.2–98.6%) and 94.7% (95% CI 89.9–97.2%), respectively (Fig. 2). Cumulative probabilities of metastasis-free survival were 98.1% (95% CI 95.1–99.3%), 97.0% (95% CI 93.4–98.6%) and 95.9% (95% CI 91.1–98.1%) at 1, 2 and 4 years, respectively.

Predictors of local recurrence and metastasis

Univariate analysis showed that tumour diameter and tumour thickness have significant association with higher risk of local recurrence. Localization on the ear and invasion of deeper structures also contributed to a higher risk, but the small number of events limited the statistical power. Prognostic factors associated with significantly increased risk of metastasis were, from highest to lowest HR: location on the ear, invasion of deeper structures, no surgical treatment, poor differentiation and tumour thickness and tumour diameter (Table II). Perineural invasion is also likely to be a contributing prognostic factor.

Our assumption that tumour diameter and tumour thickness are correlated was confirmed (R=0.33, $p<0.0001$). Therefore, we used multivariate survival analysis to evaluate the independent effect of each factor. The results show that both local recurrence and tumour

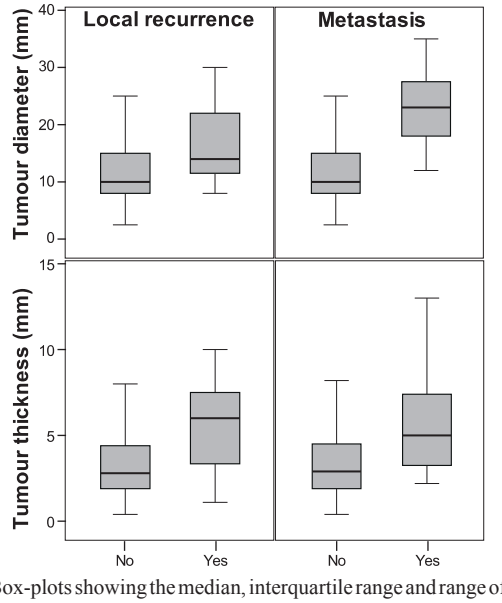

Fig. 1. Box-plots showing the median, interquartile range and range of tumour diameter and tumour thickness for patients with local recurrence and metastasis.

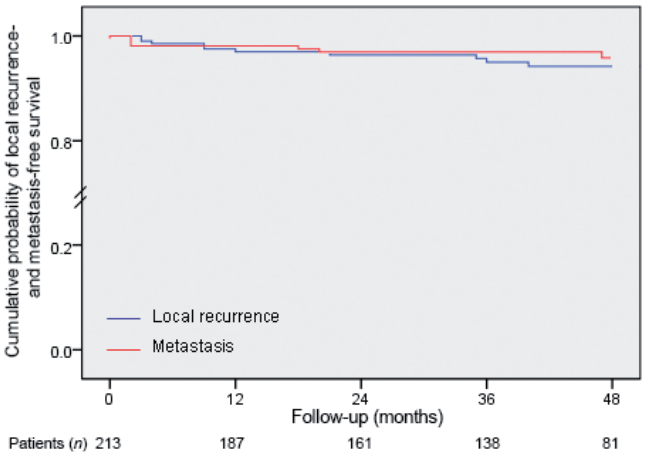

Fig. 2. Kaplan–Meier survival analysis for local recurrence and metastasis.

thickness are independent predictors (Table III). Other tumour characteristics, such as angio-invasion, perineural invasion and ulceration, were not independent predictors for metastasis or local recurrence after simultaneous adjustment for tumour diameter and tumour thickness.

DISCUSSION

This study supports the hypothesis that tumour thickness and tumour size are both important prognostic factors in cSCC at any body site. Evaluation of the independent effect of each of these 2 predictors in multivariate analysis showed that tumour diameter and tumour thickness were independent prognostic factors for local recurrence as well as for metastasis. This corroborates the findings of a large prospective study by Brantsch et al. (11).

Our results were obtained from a population of patients treated at a reference centre for dermatological oncology, which may have led to the inclusion of a selected population. This may have consequences for the calculation of the cumulative incidence of local recurrence and metastasis, but may be less relevant for the identification of risk factors. We do not expect that prognostic factors, the focus of our study, will be very different in our centre from those in other centres, because we assume that the underlying biological mechanisms are universal. In addition, we found comparable percentages of metastasis and local recurrences as those of previous studies (9, 11). The significant results with respect to prognostic factors in this study, such as invasion of deeper structures, location on the ear, poor differentiation, tumour diameter and tumour thickness, are in agreement with those of other studies (7, 11, 15, 27, 28).

Table II. *Univariate survival analysis of predictors for metastasis and local recurrence*

	Local recurrence ($n=11$)		Metastasis ($n=7$)	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Localization[a]				
Ear	3.2 (0.7–13.8)	0.123	21.3 (2.5–182.2)	**0.005**
Lip	1.5 (0.2–12.7)	0.729	–	–
Trunk/extremities	0.4 (0.1–2.2)	0.298	1.5 (0.1–23.5)	0.787
Immunosuppression	0.7 (0.3–2.0)	0.502	0.9 (0.3–2.6)	0.845
Tumour diameter, mm	1.1 (1.0–1.1)	**0.015**	1.1 (1.0–1.1)	**0.001**
Tumour thickness, mm	1.3 (1.1–1.5)	**<0.0001**	1.2 (1.1–1.4)	**0.010**
Invasion deeper structures				
Present vs. absent	4.3 (0.9–20.3)	0.065	20.8 (4.6–93.7)	**<0.0001**
Differentiation				
Poor vs. good/moderate	2.9 (0.4–23.2)	0.316	15.7 (3.5–70.3)	**<0.0001**
Perineural invasion				
Present vs. absent	2.2 (0.5–10.2)	0.328	4.4 (0.9–22.7)	0.077
Surgical treatment				
No vs. yes	4.5 (0.6–35.9)	0.151	19.9 (3.6–108.8)	**0.001**

[a]reference other head/neck.
HR: hazard ratio; CI: confidence interval. Significant values are shown in bold.

A strength of this study is that more than 95% of the necessary information was found despite the retrospective design of the study. Furthermore, there was no restriction to particular subsets of patients with cSCC, whereas other studies included only patients with moderately to poorly differentiated lesions or with lesions originating in the head and neck region (19, 28, 29). Our study included cSCCs from various parts of the body. This allowed the evaluation of a high number of histological factors judged by 3 independent observers. Finally, with a median follow-up of 43 months it is likely that the majority of all local recurrences and metastasis could be captured (13).

This study has a number of limitations. We collected data of 224 patients with a small number of local recurrences or metastasis. It is therefore possible, that small, but relevant, associations between some of the studied histopathological characteristics and prognosis of cSCC could not be detected due to lack of power. Interobserver agreement was moderate to high for tumour thickness, tumour differentiation and perineural invasion. However, interobserver agreement was poor for part of the studied histopathological characteristics.

Identification of predictors for higher risk of local recurrence and metastasis has consequences for tumour staging. Staging of cSCC is carried out according to the UICC TNM classification system. In 2009, the UICC TNM classification system was adjusted (20, 30). In case of 2 or more additional risk factors (>4 mm depth, Clark level V, perineural invasion, angio-invasion, localization on the ear or lip, and poorly or undifferentiated tumours) in T1 tumours, the tumour is classified as a stage II tumour. Comparison of the previous and present UICC TNM classification system revealed a shift from 11 patients with stage I cSCC to stage II. Two (18%) of these patients developed a local recurrence of their cSCC. This indicates that staging of cSCC is indeed relevant to define prognosis.

In this study evaluating prognostic factors of cSCC at any body site, we found additional evidence that both tumour diameter and tumour thickness are important prognostic factors for local recurrence as well as for metastasis. As metastasis can also occur outside the head and neck area, it is important to know whether prognostic variables

Table III. *Multivariate survival analysis of predictors for metastasis (*n = *7) and local recurrence (*n = *11)*

	Local recurrence		Metastasis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Tumour diameter, mm	1.1 (1.0–1.1)	0.048	1.1 (1.0–1.1)	0.018
Tumour thickness, mm	1.3 (1.1–1.5)	0.002	1.2 (1.0–1.5)	0.042

HR: hazard ratio; CI: confidence interval.

differ. To better define high- and low-risk tumours, it is important to report the diameter in the clinical file and the tumour thickness in the histological report. Omitting 1 of these 2 factors makes accurate determination of prognosis difficult. Other clinical and histopathological characteristics, such as location on the ear, poor differentiation and invasion of deeper structures, are also important in determining prognosis. Larger prospective studies are necessary to confirm these results and to identify additional clinical and mainly histopathological features that affect prognosis. Better knowledge of prognostic variables helps to define the high-risk patient who requires more radical treatment and a closer follow-up. In this respect, inclusion of tumour thickness for staging, as implemented in the adjusted UICC TNM classification system, is an important improvement.

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