# Risk factors for incomplete excision of cutaneous squamous cell carcinoma: a large cohort study

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ORIGINAL ARTICLE

# Risk factors for incomplete excision of cutaneous squamous cell carcinoma: a large cohort study

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## Abstract

**Background** The standard treatment for cutaneous squamous cell carcinoma (cSCC) is surgical excision. Failure to radically remove a cSCC is a risk for recurrence, progression and metastasis.

**Objectives** This study investigates several risk factors for incomplete excision of cSCC.

**Methods** All consecutive patients in a single institution treated with wide local excision for primary cSCC over a 10-year period were included in this study. Risk factors such as: gender, age, immunosuppression, tumour size, location, differentiation grade, tumour depth, perineural and lymphovascular invasion (PNI and LVI) were extracted from the database. Univariable and (if applicable) multivariable logistic regression analysis were used to identify risk factors ($P < 0.05$). Generalized estimating equations (GEEs) were used for multiple tumours within the same patients.

**Results** A total of 566 patients with 1159 cSCC were identified. Univariable and multivariable logistic regression analysis showed that depth beyond the dermis (OR: 5.7 95% CI: 3.1–10.5) was the only risk factor for incomplete excision of cSCC. Immunosuppression was only a risk factor in the deep plane (OR: 2.5, 95% CI: 1.3–4.6).

**Conclusion** Tumour depth beyond the dermis is the most important risk factor for incomplete excision of cSCC. Immunosuppression is a risk factor in the deep plane but its relevance is uncertain. Immunosuppression is not consistently included in the current cSCC staging systems, but care should be taken when treating these patients.

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## Conflicts of interest

The authors declare no conflict of interest

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## Introduction

The primary treatment for cutaneous squamous cell carcinoma (cSCC) is surgical excision, with tumour-free resection margins in the peripheral and deep planes. Failure to radically remove a cSCC increases the risk of recurrence, progression and metastasis.[1–4]

Several risk factors have been identified that are associated with incomplete excision such as[5]: location on the head and neck,[6–8] tumour differentiation,[9] tumour size,[2,8,10,11] tumour thickness[8] and the physician who performs the surgery (e.g. general physician, dermatologist or plastic surgeon) and their experience.[10,12,13]

It remains unclear if immunosuppression is a risk factor for incomplete excision but it is recognized as a risk factor for cSCC development and poor outcome. Studies in organ transplant recipients show that they develop more cSCC, and in the case of in-transit metastases have increased morbidity and mortality.[14] Therefore, cSCC in patients with immunosuppression are recognized as high-risk tumours in current guidelines, but this risk factor is not incorporated in the tumour staging systems.

Recommendation for surgical margins for cSCC with wide local excision differs among guidelines. An European guideline advises for low-risk tumours a margin of 5 mm. For high risk

tumours a safety margin of 6–10 mm is suggested. The depth should include the subcutaneous tissue.[15] The American guideline (based on the National Comprehensive Cancer Network, NCCN, USA) advises peripheral excision margins for low-risk cSCC of 4–6 mm and a depth in the mid-subcutaneous adipose tissue.[16] High-risk tumours are recommended to be operated with Mohs Micrographic Surgery (MMS). Most cSCC are however, still treated by conventional wide local excision because MMS is not available in all medical centres.[15] It remains difficult to advise surgical margins for high-risk tumours due to limited data. Another problem is that there is a variation in risk factors between different tumour staging systems. For example, the American Joint Committee on Cancer (AJCC), NCCN and Brigham and Women's Hospital BWH system categorize cSCC into low- and high-risk tumours.[17] The AJCC and NCCN do categorize immunosuppression as a high-risk tumour but immunosuppression is not considered in their TNM clinical classification systems. Only tumour-specific factors are included in the classification systems and the role of patient characteristics such as immunosuppression therefore, remains unclear.

This study investigates several risk factors in incomplete excision of cSCCs in a large cohort of patients treated by wide local excision.

## Materials and Methods

All consecutive patients with primary cSCC treated with wide local excision were identified over a 10-year period from January 2004 to December 2013 from the institutional oncology and pathology databases of the Leiden University Medical Centre. The patient records used are from a previously made database.[18] cSCC which were treated with curettage and coagulation were not included in this study. Patient data were extracted from the institutional oncology database and medical records. Immunosuppressed patients were defined as: solid organ transplant recipients (OTR) and patients with immunosuppressive drugs due to chronic rheumatic diseases, inflammatory bowel disease or patients with hematologic malignancies (e.g. chronic lymphocytic leukaemia). Tumour size, location, differentiation grade, depth of invasion, perineural invasion (PNI) and lymphovascular invasion (LVI) were retrieved for all tumours from the Dutch pathology registry (PALGA). Unless stated otherwise in the pathology report, tumours were considered to be free of PNI and LVI.

Excision margins of the Dutch cSCC guideline were followed, which is comparable with the European EDF–EADO–EORTC consensus group, using 5 mm margin for low risk cSCC and at least 10 mm for high risk cSCC.

Descriptive statistics were applied for patient and tumour characteristics. Continuous data will be reported as mean with standard deviation or median with interquartile range, and categorial data as number with percentage. Univariable and multivariable logistic regression analysis were used to identify risk factors for incomplete excision. Incomplete excision was defined as having confirmed histological positive surgical margins in the side or deep plane. The logistic regression was performed at the tumour level and outcomes of multiple excision within the same patient were taken into account using generalized estimating equations (GEE) with an independent working correlation. A *P*-value of <0.05 was set as statistically significant for all analyses. Multiple imputation method with 20 sets was used for missing values in the multivariable logistic regression analysis. Statistical analysis was performed using SPSS version 25 (SPSS, Chicago, Illinois, USA).

## Results

A total of 566 patients (350 male, 216 female) were identified in the study period with a total of 1159 primary excised cSCC. Tumour characteristics and radical or incomplete frequencies are shown in Table 1. The mean age when patients presented with their first cSCC was 69.4 years (range 22–97). There were 139 patients with an immunosuppressed state (24.6%): 78 patients (13.8%) had received an organ transplant and 61 (10.8%) were immunosuppressed for other reasons. In these immunosuppressed patients, 423 cSCC had been excised: 315 in OTR and 108 in patients with immunosuppression for other reasons.

Of the 1159 cSCC, 106 (9%) were incompletely excised. In 49 (46.2%) cSCC, only the side margins were involved and in 37 (34.9%), only the deep margins were positive. In 20 (18.9%) cSCC, both side and deep margins were positive.

A complete overview of the univariable and multivariable analyses for risk factors for incomplete excision of cSCC is shown in Table 2. The overall univariable GEE analysis showed that immunosuppression (only OTR) (OR: 2.2, 95% CI: 1.2–4.0, $P = 0.08$), tumour depth beyond the dermis (OR: 6.5, 95% CI: 3.6–11.9, $P < 0.01$) and perineural invasion (OR: 5.7, 95% CI: 1.9–17.7, $P = 0.02$) were risk factors correlated to incomplete excision of cSCC. The multivariable GEE analysis showed that only depth beyond the dermis (OR: 5.7, 95% CI: 3.1–10.5, $P < 0.01$) was the remaining risk factor for incomplete excision of cSCC.

The incomplete excisions were further divided in the level of irradicality, i.e: side ($N = 49 + 20$), depth ($N = 37 + 20$) or both ($N = 20$) planes. An overview of the GEE analysis is shown in Table 3. Univariable GEE analysis of the side margins showed location head and neck (OR: 2.4, 95% CI: 1.1–5.2, $P = 0.03$), depth beyond the dermis (OR: 3.3, 95% CI: 1.7–6.2, $P < 0.01$), perineural invasion (OR: 9.1, 95% CI: 2.8–29.4, $P < 0.01$) and lymphovascular invasion (OR: 7.8, 95% CI: 1.4–44.3, $P = 0.02$) as risk factors. Multivariable GEE analysis of the side margins showed depth beyond the dermis (OR: 2.5, 95% CI: 1.3–4.9, $P < 0.01$) and PNI (OR: 3.9, 95% CI: 1.1–14.4, $P = 0.04$) as risk factors.

Univariable GEE analysis of the deep margins showed immunosuppression (both OTR and other immunosuppression) (OR:

**Table 1** Tumour characteristics

| | | Total *N* (%) 1159 | Radical *N* (%) 1053 | Incomplete *N* (%) 106 |
|---|---|---|---|---|
| **Location** | Head and neck | 762 (65.8) | 680 (64.6) | 82 (77.4) |
| | Trunk | 104 (9.0) | 97 (9.2) | 7 (6.6) |
| | Upper extremity | 179 (15.4) | 163 (15.5) | 16 (15.1) |
| | Lower extremity | 114 (9.8) | 113 (10.7) | 1 (0.9) |
| **Tumour size, mm** | Median-mean (range) | 10–12.6 (2–75) | 10–12.4 (2–75) | 12–14.6 (3–45) |
| | ≤20 | 935 (80.7) | 851 (80.9) | 84 (79.2) |
| | >20 | 131 (11.3) | 110 (10.4) | 21 (19.8) |
| | Missing | 93 (8.0) | 92 (8.7) | 1 (1.0) |
| **Differentiation** | Well | 795 (68.6) | 718 (68.2) | 77 (72.6) |
| | Moderate | 171 (14.8) | 161 (15.3) | 10 (9.4) |
| | Poor | 118 (10.2) | 105 (10.0) | 13 (12.3) |
| | Undifferentiated | 57 (4.9) | 52 (4.9) | 5 (4.7) |
| | Missing | 18 (1.6) | 17 (1.6) | 1 (1.0) |
| **Depth** | Papillary dermis | 10 (0.9) | 10 (0.9) | 0 |
| | Reticular dermis | 27 (2.3) | 27 (2.6) | 0 |
| | Dermis unspecified | 869 (75.0) | 824 (78.2) | 45 (42.5) |
| | Subcutis | 190 (16.4) | 143 (13.6) | 47 (44.3) |
| | Fascia | 3 (0.3) | 1 (0.1) | 2 (1.9) |
| | Cartilage | 16 (1.4) | 12 (1.1) | 4 (3.8) |
| | Muscle | 24 (2.1) | 16 (1.5) | 8 (7.5) |
| | Bone | 1 (0.1) | 1 (0.1) | 0 |
| | Missing | 19 (1.6) | 19 (1.8) | 0 |
| **Perineural invasion** | Yes | 14 (1.2) | 9 (0.9) | 5 (4.7) |
| | No | 1145 (98.8) | 1044 (99.1) | 101 (95.3) |
| **Vasoinvasion** | Yes | 6 (0.5) | 4 (0.4) | 2 (1.9) |
| | No | 1153 (99.5) | 1049 (99.6) | 104 (98.1) |

2.8, 95% CI: 1.5–5.1, $P < 0.01$), tumour depth beyond the dermis (OR: 40.8, 95% CI: 17.4–77.8, $P < 0.01$), PNI (OR: 8.8, 95% CI: 2.6–29.5, $P < 0.01$) and LVI (OR: 9.5, 95% CI: 1.7–52.5, $P < 0.01$) as risk factors. Multivariable GEE analysis of the deep margins showed immunosuppression (both OTR and other) (OR: 2.5, 95% CI: 1.3–4.6, $P < 0.01$) and depth beyond the dermis (OR: 38.2, 95% CI: 15.3–95.5, $P < 0.01$).

Univariable GEE analysis of both margins showed immunosuppression (only OTR) (OR: 3.1 95% CI: 1.2–8.2, $P = 0.03$), tumour size >20 mm (OR: 3.1, 95% CI: 1.1–8.4, $P = 0.03$), tumour depth beyond the dermis (OR: 43.0, 95% CI: 9.7–191.3, $P < 0.01$), PNI (OR: 29.0, 95% CI: 7.8–107.7, $P < 0.01$) and LVI (OR: 29.2, 95% CI: 5.0–170.5, $P < 0.01$) as risk factors. Multivariable GEE analysis of both margins showed immunosuppression (only OTR) (OR: 3.3, 95% CI: 1.3–8.5, $P = 0.04$), depth beyond the dermis (OR: 35.0, 95% CI: 7.0–175.4, $P < 0.01$) and PNI (OR: 7.8, 95% CI: 1.4–45.1, $P = 0.02$).

In total, 26 (2.2%) cSCC metastasized during the follow-up period. Univariable analysis showed that incomplete excision has an odds ratio of 3.9 (95% CI: 1.6–9.4) for metastasis. Due to the low amount of events, further multivariable logistic regression analysis was not possible.

## Discussion

In this cohort study, we found a 9.1% incomplete excision rate for cSCC. A recent estimation in the literature showed data of 13% incompletely excised of cSCC.[5] Depth beyond the dermis was found as an independent risk factor for overall incomplete excision. PNI was found as a risk factor for the side margins and immunosuppression for the deep margins. A threefold higher risk for metastasis was calculated after an incomplete excision.

Our study did not find the known risk factors for incomplete excision of cSCC such as location in the head and neck area, tumour depth and size, invasive growth and re-excision[5,] and instead only found depth beyond the dermis as a risk factor. This remains significant for all incomplete margins (side, deep and both) and is more important than, for example the size of the lesion.[6,12,19–22] This could be explained by guidelines which advise for peripheral margins, based on the size of the cSCC, to obtain complete excision.[15,16,23] The tumour depth however is often not recognized or incompletely identified in biopsies and

**Table 2** Risk factors for incomplete excision of cSCC

| Patient characteristics | | Univariable GEE analysis OR (95% CI) | Multivariable GEE analysis OR (95% CI) |
|---|---|---|---|
| Gender | | | |
| | Male | 1 (reference) | |
| | Female | 0.45 (0.22–0.89)* | 0.57 (0.29–1.1) |
| Patient age, year | | | |
| | Median-mean-range | 0.98 (0.96–1.0) | 0.99 (0.96–1.0) |
| Immunosuppression | | | |
| | No | 1 (reference) | |
| | Yes | 2.2 (1.2–3.9)* | 1.8 (0.85–3.7) |
| | Transplantation | 2.2 (1.2–4.0)* | 1.7 (0.73–4.1) |
| | IS other only | 2.3 (0.94–5.4) | 1.9 (0.81–4.7) |
| **Tumour characteristics** | | | |
| Location | | | |
| | Trunk/extremities | 1 (reference) | |
| | Head and neck | 1.9 (0.94–3.7) | 1.6 (0.83–2.9) |
| Tumour size | | | |
| | ≤20 mm | 1 (reference) | |
| | >20 mm | 1.4 (0.85–2.4) | 1.1 (0.58–2.0) |
| Differentiation | | | |
| | Well-moderate | 1 (reference) | |
| | Poor-undiff | 1.1 (0.60–2.2) | 0.96 (0.49–1.9) |
| Depth | | | |
| | Dermis | 1 (reference) | |
| | Beyond dermis | 6.5 (3.6–11.9)* | 5.7 (3.1–10.5)* |
| Perineural invasion | | | |
| | No | 1 (reference) | |
| | Yes | 5.7 (1.9–17.7)* | 2.0 (0.53–7.8) |
| Lymfovascular invasion | | | |
| | No | 1 (reference) | |
| | Yes | 5.0 (0.92–27.7) | 1.8 (0.23–14.3) |

*$P < 0.05$.

has usually just been seen in the complete excision specimen. In other words, the true depth of the cSCC is identified after the excision and has less influence on the peri-operative excision margin. This principle also accounts for PNI. Furthermore, there are few recommendations for the deep plane. Low-risk primary cSCC can be excised in the mid-subcutaneous adipose tissue or complete hypodermis[24] while other authors preclude a recommendation due to insufficient data for high-risk tumours.[16] Due to a lack of definite advise for high-risk cSCC, care should be taken in the deep plane.

Immunosuppression is only seen as a risk factor, when categorizing the incomplete margins into the: side, deep and both margins. Only two previous studies investigated the risk of immunosuppression for incomplete excision with opposite results. Kjerkegaard and Stolle compared OTRs with non-OTRs and calculated no significant difference in incomplete excision rate.[19] However, their study had a small sample of only six OTR patients out of 437 patients. Stewart and Saunders analysed 264 patients using immunosuppression, which is roughly 18% of their total study population and found that it was not a predictive factor.[8] In comparison, in our study, 36% of the analysed tumours were from patients using immunosuppression, which represents a representative group. In our opinion, this is an important finding, as OTR and other immunosuppressed patients have a risk for local recurrence and metastatic cSCC. Our expectation however, was that OTR and immunosuppression would also be a risk factor for the side margins, as the side margins are often difficult to see due to poor skin condition and actinic keratosis. But this was not the case in our analysis and the relevance of our results remains unclear.

Some limitations should be noted. First, the retrospective design of the study has a few drawbacks. The excision margins advised in the Dutch cSCC guideline were followed, but excisions were carried out by different physicians (mainly by medical specialists such as dermatologists and plastic surgeons) and this could give variation in the excision margins that were used. The histopathological examination was performed by different pathologists and was not systematically reviewed, although the pathology reports follow the Dutch cSCC guideline. For this reason, data may be subject to interobserver variation. Moreover, not all data were complete and missing data were replaced by imputed values. Furthermore, all of the cSCC were excised in a tertiary referral hospital, that could have introduced a selection bias.

Our study confirmed that incomplete excision is a risk factor for metastasis and shows the importance for future guidelines.[25] Surgical margins are currently recommended based on peripheral margins. As stated before, guidelines for cSCC do not define a recommendation for the deep plane. MMS could eliminate the risk of incomplete excision of the deep plane in high-risk cSCC. However, this technique is not always available. A study by Kofler *et al.* shows that even with complete circumferential peripheral and deep margin assessment after local wide excision, a local recurrence rate for cSCC of 5.4% exists.[26]

Our data show that the depth of the tumour is the most important risk factor for incomplete excision of cSCC. Care should be taken in the deep plane in patients with an immunosuppressive state. These risk factors should be known prior to surgery and adequate measures should be taken when performing a wide local excision cSCCs.

**Table 3** Univariable (UV) and multivariable (MV) GEE analysis for the side, deep and both planes in incomplete excisions of cSCC

| Patient characteristics | | Incomplete side margins (*N* = 69) | | Incomplete deep margins (*N* = 57) | | Incomplete both margins (*N* = 20) | |
|---|---|---|---|---|---|---|---|
| | | Univariable GEE OR (95% CI) | Multivariable GEE OR (95% CI) | Univariable GEE OR (95% CI) | Multivariable GEE OR (95% CI) | Univariable GEE OR (95% CI) | Multivariable GEE OR (95% CI) |
| Gender | | | | | | | |
| | Male | 1 (reference) | | | | | |
| | Female | 0.56 (0.68–1.2) | | 0.46 (0.20–1.1) | | | |
| Patient age, year | | | | | | | |
| | Median-Mean-range | 0.98 (0.96–1.0) | | 0.98 (0.95–1.0) | | 0.97 (0.93–1.0) | |
| **Immunosuppression** | | | | | | | |
| | No | 1 (reference) | | | | | |
| | Yes | 1.9 (0.89–4.1) | 1.9 (0.83–4.2) | 2.8 (1.5–5.1)* | 2.5 (1.3–4.6)* | 2.8 (1.1–7.1)* | 2.7 (1.0–6.8)* |
| | Transplantation | 2.1 (0.95–4.8) | 2.1 (0.92–5.0) | 2.5 (1.3–4.8)* | 2.2 (1.1–4.3)* | 3.1 (1.2–8.2)* | 3.3 (1.3– 8.5)* |
| | IS other only | 1.3 (0.48–3.6) | 1.0 (0.93–3.1) | 3.5 (1.4–9.0)* | 3.5 (1.2–9.7)* | 1.8 (0.39–8.9) | 0.49 (0.07–3.2) |
| **Tumour characteristics** | | | | | | | |
| Location | | | | | | | |
| | Trunk/extremities | 1 (reference) | | | | | |
| | Head and neck | 2.4 (1.1–5.2)* | 2.1 (0.89–5.0) | 1.3 (0.60–2.8) | 0.88 (0.42–1.9) | 1.3 (0.4–3.7) | 0.63 (0.19–2.0) |
| Tumour size | | | | | | | |
| | ≤20 mm | 1 (reference) | | | | | |
| | >20 mm | 1.6 (0.9 – 3.0) | 1.4 (0.72–2.8) | 1.7 (0.85–3.3) | 0.94 (0.40–2.2) | 3.1 (1.1–8.4)* | 1.5 (0.40–5.6) |
| Differentiation | | | | | | | |
| | Well-moderate | 1 (reference) | | | | | |
| | Poor-undiff | 1.2 (0.54–2.7) | | 1.0 (0.43–2.3) | | 0.95 (0.27–3.3) | |
| Depth | | | | | | | |
| | Dermis | 1 (reference) | | | | | |
| | Beyond dermis | 3.3 (1.7–6.2)* | 2.5 (1.3–4.9)* | 40.8 (17.4–77.8)* | 38.2 (15.3–95.5)* | 43.0 (9.7–191.3)* | 35.0 (7.0–175.4)* |
| Perineural invasion | | | | | | | |
| | No | 1 (reference) | | | | | |
| | Yes | 9.1 (2.8–29.4)* | 3.9 (1.1–14.4 )* | 8.8 (2.6–29.5)* | 2.3 (0.5–10.2) | 29.0 (7.8–107.7)* | 7.8 (1.4–45.1)* |
| Lymfovascular invasion | | | | | | | |
| | No | 1 (reference) | | | | | |
| | Yes | 7.8 (1.4–44.3)* | 2.0 (0.21–18.8) | 9.5 (1.7–52.5)* | 2.2 (0.2–23.6) | 29.2 (5.0–170.5)* | 3.0 (0.1–80.2) |

*$P < 0.05$.

## Conclusion

Tumour depth beyond the dermis is the most important risk factor for incomplete excision of cSCC. Immunosuppression is a risk factor for an incomplete deep margin and although the relevance is not completely clear, care should be taken when treating these patients.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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