# Rate and characteristics of incompletely excised cutaneous squamous cell carcinoma: a large prospective study, systematic review and meta-analysis

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## ABSTRACT

Background: Incomplete excision of cutaneous squamous cell carcinoma (cSCC) has been associated with an increased risk of recurrence, metastasis and mortality.

Objectives: To determine the rate and characteristics of incompletely excised cSCC.

Methods: Prospective study of all patients who gave their informed consent, with a cSCC treated with standard excision (SE) at one of six Departments of Dermatology in the Netherlands between 2015 and 2017. Pathology reports were screened to detect all incompletely excised cSCCs. Additionally, a systematic review was conducted with pooled average estimate of incompletely excised cSCC.

Results: A total of 592 patients with 679 cSCCs were included whereby the majority of cases were low risk cSCC (89%). The rate of incompletely excised cSCC was 4% (n = 26) and all were high risk cSCC of which 24 invaded the deep excision margin. The systematic review included 36 studies (n = 11,235 cSCCs) of which the majority was retrospectively designed (n = 31). The included studies used heterogenic inclusion criteria, different excision margins and heterogenic treating physicians. The pooled average estimate of incompletely excised cSCC was 12% (95% confidence interval 10-16, $I^2$=92%, range 0-39%).

Conclusions: Conclusions on the efficacy of SE for cSCC must be made carefully. Although the current prospective study showed that the risk of an incompletely excised cSCC was low (4%) for a cohort that was dominated by low risk cSCCs, the systemic review showed a wide range of rate of incompletely excised cSCC among studies that included heterogenic cases.

## INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer after basal cell carcinoma (BCC).[1-4] At least one per 15 Caucasians will develop a cSCC before the age of 85 and the incidence is still rising.[1-4]

In The Netherlands, cSCC is commonly treated with standard excision (SE).[5] The rate of incompletely excised cSCC is an important indicator for the quality of care. Incompletely excised cSCC has been associated with an increased risk of recurrence and, although rare, with metastasis and disease-specific death.[6-8] Therefore, it is recommended to re-excise residual cSCC.[5-11] For the patient, a re-excision is injurious because it can lead to local functional and aesthetic comorbidity. For society, a re-excision leads to higher costs.

To prevent incompletely excised cSCC and to decrease cSCC recurrence rates, in America it is generally accepted that Mohs micrographic surgery (MMS) is indicated for both T1 and T2 cSCC.[12] While in the Dutch cSCC guideline from 2012, MMS was only mentioned as an alternative to SE if SE would lead to extensive functional or aesthetic comorbidity.[5] Since a recent update of the Dutch cSCC guideline, MMS is only indicated as appropriate for facial cSCC (T1 and T2) when it is aimed to preserve the healthy tissue and thereby to decrease the functional or aesthetic comorbidity.[13]

The rate of incompletely excised cSCC varies widely among studies whereby the studies are mainly retrospectively designed and use heterogenic inclusion criteria.[14] Therefore, conclusions on the efficacy of SE for cSCC are inconsistent. To assess the efficacy of SE for cSCC, this study determined the rate and detailed characteristics of incompletely excised cSCC in a prospectively designed multicentre observational study and in a systematic review with meta-analysis. This study is part of an on-going observational study that compares the efficacy of MMS with SE regarding rates of recurrences, metastasis and disease specific death.

## METHODS

This was a prospective study of all patients who gave their informed consent, with a cSCC treated with SE at the Department of Dermatology in one of six study centres (two tertiary care hospitals, three secondary care hospitals and one private practice) in the Netherlands between 1 January 2015 and 31 December 2017. This study is part of an on-going observational study (i.e. not randomized) which compares MMS with SE for cSCC

regarding rates of recurrence, metastasis, and disease specific death after follow-up of at least five years. The inclusion period of this study closed on 31 December 2017 while the follow-up is ongoing. The study was exempted from approval by all institutional review boards.

Inclusion criteria were excisions of invasive cSCCs, i.e. cSCC of all body sites, primary and recurrent or previously incompletely excised cSCC. Multiple cSCCs per patient were included if located in different anatomical subunits according to the New York Classification. For the current study, we excluded all cSCCs that were treated with MMS. In each study centre, SE and MMS was available during the inclusion period. Since specific indication criteria for the use of SE or MMS for cSCC were lacking in the Dutch cSCC guideline of 2012, the treating dermatologist decided together with the patient which surgical treatment would be used (i.e. SE or MMS) whereby MMS was offered to patients with a cSCC of the head and neck or other area's (e.g. hands) if SE would lead to extensive functional or aesthetic comorbidity.[5]

Dermatologists recorded the following variables prospectively in a digital standardized study form: patient age, gender and immune status, tumour location, location in the H-zone of the face, surgical history, clinical tumour size, excision margin in mm, defect depth, whether the reconstruction was delayed until the result of the histology report and how the defect was reconstructed.

Dermatologists recorded the conclusions of the pathologist concerning the histological tumour free margins, invasion depth in mm, differentiation, and perineural or lymphovascular invasion. The outcome of interest was an incompletely excised cSCC. According to the Dutch cSCC guideline, an incomplete excision was defined as histological cSCC extending to the inked surgical margin or in case of a ≥ T2 cSCC with a histological tumour free margin < 2 mm.[5,13] The eight edition of the American Joint Committee on Cancer (AJCC) system was used to stage the cSCCs whereby T1 cSCCs were classified as cSCCs at low risk of poor outcome and ≥ T2 as high risk cSCCs.[15]

Excisions were performed in a standard manner by a dermatologist (n = 29) or resident (n = 54) under supervision of a dermatologist. Specimens were postoperatively assessed by a pathologist (n = 25) with the standard vertical bread loaf technique and haematoxylin and eosin staining. Pathologists did not know if specimens were included in the study.

### Statistics

Descriptive statistics were used to report the baseline characteristics of patients, cSCC, treatment and study outcome. Risk factors for an incomplete excision were not assessed with logistic regression due to small subgroups through which the risk analysis would be underpowered. SPSS 24.0 for windows (SPSS Inc., Chicago, IL) was used for statistical analyses.

### Systematic literature review and meta-analysis

The systematic review was conducted and reported according to the MOOSE guidelines for meta-analysis of observational studies. The protocol for this systematic review was recorded in the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42018096312.

In this systematic review, the following databases were searched: Embase, Medline Ovid, Web of science, Cochrane Central, and Google scholar from inception of the databases to 5 May 2018, for original articles in English reporting on the rate of incompletely excised cSCC . Additionally, the bibliography of included studies and previously published review articles were checked for other relevant articles. Articles were included if the rate of incomplete excision was specific for cSCC (i.e. not mixed with other tumours or in situ cSCC) and standard excision (i.e. not mixed with other treatment modalities). Articles were excluded if they were non-English, if the full text was not available, if the study was not original, or if the study included less than five cases.

Two review authors (CBL, AP) independently screened the titles and abstracts. Full texts were reviewed of those articles which potentially met the inclusion criteria. After consensus was reached on the included articles, data was extracted by the two reviewers independently, using standardized extraction forms. Risk of bias of individual studies could not be evaluated because of the lack of a relevant validated tool.

Raw proportions of incompletely excised cSCC were calculated for each study (events divided by the total number of included cSCCs). The pooled average estimates of incomplete cSCC excision was calculated using a random effect model with 95% CI. Index $I^2$ was used to quantify the impact of heterogeneity and to assess inconsistency. R studio (R core team, Vienna, Austria) was used for the meta-analysis.

## RESULTS

### Results of the prospective study

A total of 592 patients (348 man, overall median age 76 years, IQR 69-82) with 679 cSCCs were included (Table 1). Overall, 90% (n = 533) of the patients had one cSCC, 7% (n = 42) had two cSCCs, and 3% (n = 17 ) had three or more cSCCs.

**Table 1.** Differences between completely and incompletely excised cutaneous squamous cell carcinoma.

| | Completely excised cSCC n (%) | Incompletely excised cSCC n (%) |
|---|---|---|
| **Patient characteristics, n = 592** | 569 (96) | 23 (4) |
| Sex | | |
| Men | 333 (59) | 15 (65) |
| Women | 236 (42) | 8 (35) |
| Age in years, median IQR | 76 (69-82) | 76 (68-81) |
| Immunosuppression | | |
| No | 505 (89) | 20 (87) |
| Yes | 64 (11) | 3 (13) |
| **cSCC characteristics, n = 679** | 653 (96) | 26 (4) |
| Location | | |
| Body | 288 (44) | 3 (12) |
| Head and neck not H-zone | 219 (36) | 16 (62) |
| H-zone | 146 (22) | 7 (27) |
| Clinical size | | |
| 0-20 mm | 628 (96) | 16 (62) |
| ≥21 mm | 25 (4) | 10 (39) |
| Surgical history | | |
| Primary | 626 (96) | 25 (96) |
| Recurrent/incompletely excised | 27 (4) | 1 (4) |
| Invasion depth | | |
| ≤ 6 mm | 446 (68) | 11 (42) |
| > 6 mm | 16 (3) | 11 (42) |
| Unspecified | 191 (29) | 4 (15) |
| Differentiation | | |
| Well or moderate | 523 (80) | 14 (54) |
| Poor | 130 (20) | 12 (46) |
| PNI or lymphovascular invasion | | |
| Not visible | 635 (97) | 14 (54) |
| Yes | 18 (3) | 12 (46) |

**Table 1.** (continued)

| | Completely excised cSCC n (%) | Incompletely excised cSCC n (%) |
|---|---|---|
| High risk cSCC | | |
| No | 601 (92) | 0 |
| Yes[a] | 52 (8) | 26 (100) |
| **Procedural characteristics, n = 679** | 653 (96) | 26 (4) |
| Excision margin | | |
| ≤ 5 mm | 627 (96) | 16 (62) |
| > 5 mm | 26 (4) | 10 (39) |
| Excision margin[b] | | |
| Conform Dutch guideline | 622 (95) | 14 (54) |
| Wider | 16 (3) | 6 (23) |
| Smaller | 15 (2) | 6 (23) |
| Defect depth | | |
| Dermis | 526 (81) | 17 (65) |
| Deep | 127 (19) | 9 (35) |
| Timing of reconstruction | | |
| Directly after the excision | 619 (95) | 18 (69) |
| Delayed[c] | 34 (5) | 8 (31) |
| Reconstruction type | | |
| Simple[d] | 601 (92) | 19 (73) |
| Complex[e] | 52 (8) | 7 (27) |

Percentages were rounded.

cSCC, cutaneous squamous cell carcinoma; IQR, inter quartile range; mm, millimetre; n, number; PNI, perineural invasion.

[a] High risk cSCC include ≥T2 cSCC according to the eight edition of the American Joint Committee on Cancer staging system.[15]

[b] According to the Dutch cSCC guideline five mm for T1 cSCC, and ten mm for ≥T2 cSCC.[5,13]

[c] Delayed reconstruction until the result of the histology report.

[d] Simple reconstruction include primary closure or healing by secondary intention.

[e] Complex reconstruction include all non-simple reconstructions, e.g. flaps and grafts.

Of the 679 cSCCs, location was in the head and neck in 57% (n = 388), of which cSCCs were most commonly located on the scalp 18% (n = 119), peri-auricular area 10% (n = 65) and forehead 9% (n = 58). CSCCs were located outside the head and neck in 43% (n = 291), locations were: leg 13% (n = 85), arm 10% (n = 69), trunk 10% (n = 68), hand 9% (n = 59), and feet 2% (n = 10).

The majority of cSCC were excised with a margin conform to the Dutch cSCC guideline (94%).[5,13] Although the Dutch cSCC guideline recommends to take a punch biopsy to histologically diagnose a skin tumour to plan an optimal treatment strategy, 17%

(n = 117) excisions were performed without prior biopsy.[5,13] Of the 562 excisions with prior histology (i.e. punch biopsy or previous excision), in 17% (n = 93) no cSCC was detected on the histology of the excised specimen (e.g. tumour cells could be missed due to the vertical bread loaf technique or the immune system eliminated the cSCC).

CSCCs were incompletely excised in 4% (26/679) which were all high risk cSCC (i.e. T2), while only a few completely excised cSCC were high risk tumours (52/653). The rate of incompletely excised cSCC did not differ between the six study centres (p = 0.277). Of the 26 incompletely excised cSCC, 77% (n = 20) involved the deep margin, 15% (n = 4) involved both deep and side margins, and 8% (n = 2) involved the side margin. CSCC invaded the margin in ten patients, and the histological tumour free margin was < 2 mm in 16 patients. Eight of these 16 patients with an incompletely excised cSCC did not receive an additional treatment. The other 18 patients were additionally treated with re-excision (n = 10) or MMS (n = 8).

**Results of the systematic review and meta-analysis**

The systematic review included 36 observational studies[11,16-50] including the current study (Table 2, Figure 1). A total of 11,235 cSCCs were included in the review. Study size varied from 13 to 2,536 tumours, with a median of 91. The majority of included studies had a retrospective design (n = 31). The studies used different definitions for incomplete excision (i.e. unspecified, or cSCC extending to the inked surgical margin and/or cSCC close to the surgical margin on histology). Of the 36 studies, 22 included all locations, four included only head and neck cSCCs, two included only periocular cSCCs, one included only lip cSCCs, and the location was unspecified in seven studies. Of the 36 studies, 24 included only primary cSCCs, one included only re-excisions, four included both primary cSCCs and re-excisions, and the surgical history was unspecified in six studies. Only ten of the studies reported the used excision margin, which ranged from one up to ten mm. The excisions were performed by dermatologists in seven studies, by other hospital based specialties in 18 studies (i.e. plastic surgeons, general surgeons, ophthalmologists or ENT physicians), by general practitioners in six studies, and by a mixed group of physicians in five studies. One third of the studies were performed in the United Kingdom (n = 13), seven in Australia, three in New Zealand, three in the United states of America, three in The Netherlands, and seven in other countries.

The pooled average estimate of incompletely excised cSCC was 12% (95% CI 10-16, $I^2$ 92%, range 0-39%) (Figure 2). From the seven studies that reported which margins were tumour positive, six reported that the majority of incompletely excised cSCCs involved the deep margin and one reported that the lateral margins were more often involved.

**Table 2.** Overview of included studies.

| Study | Total cSCC included n = 11,235 | Incompletely excised cSCC % range 0-39% | Location | Surgical history | Excision margin |
|---|---|---|---|---|---|
| Ang 2004 | 63 | 16 | All | Primary | 4-6 mm |
| Babington 2003 | 51 | 28 | Lip | Primary | Unspecified |
| Baker 2001 | 227 | 7 | Head and neck | Primary | Unspecified |
| Bhatti 2006 | 260 | 31 | All | Primary | Unspecified |
| Bogdanov 2005 | 369 | 7 | All | Primary | 3-6 mm |
| Bovill 2009 | 676 | 18 | All | Primary | Unspecified |
| Bovill 2012 | 84 | 29 | All | Re-excision | Unspecified |
| Chan 2011 | 82 | 9 | All | Primary | Unspecified |
| Cook 1993 | 478 | 12 | Unspecified | Primary | Unspecified |
| Corwin 1997 | 28 | 36 | All | Primary | Unspecified |
| Cox 1992 | 18 | 8 | All | Primary | Unspecified |
| Delaney 2012 | 880 | 16 | Unspecified | Primary | Unspecified |
| Fernández 2006 | 117 | 5 | Unspecified | Unspecified | Unspecified |
| Griffiths 2002 | 93 | 4 | All | Primary | Unspecified |
| Hansen 2009 | 2536 | 6 | Unspecified | Primary | Unspecified |
| Haw 2014 | 114 | 21 | Unspecified | Primary | Unspecified |
| Immerman 1983 | 84 | 29 | All | Primary | Unspecified |
| Jowkar 2015 | 58 | 16 | Head and neck | Primary | 5 mm |
| Khan 2013 | 633 | 8 | All | All | 4-6 mm |
| Matteucci 2011 | 30 | 13 | Unspecified | Unspecified | Unspecified |
| Mirshams 2010 | 273 | 18 | All | All | Unspecified |
| Mourouzis 2009 | 218 | 12 | Periocular | Primary | 5 mm |
| Nemet 2006 | 68 | 25 | Periocular | Primary | 5 mm |
| Pua 2009 | 69 | 0 | All | Primary | >5 mm |
| Ribero 2016 | 81 | 17 | All | Unspecified | >4 mm |
| Riml 2013 | 89 | 6 | All | Unspecified | 5 mm |
| Robertson 2018 | 848 | 3 | All | Primary | Unspecified |
| Seretis 2010 | 54 | 6 | Head and neck | Primary | >4 mm |
| Stewart 2014 | 81 | 6 | All | Unspecified | >4 mm |
| Stewart 2018 | 954 | 9 | All | Unspecified | Unspecified |
| Tan 2007 | 480 | 6 | All | Primary | Unspecified |
| Thomas 1994 | 54 | 11 | Unspecified | Primary | Unspecified |
| Thomas 2003 | 38 | 0 | All | Primary | 1-4 mm |
| van Lee 2018 | 355 | 18 | Head and neck | All | Unspecified |
| van Rijsingen 2015 | 13 | 39 | All | Primary | Unspecified |
| Current study | 679 | 4 | All | All | 1-10 mm |

Percentages were rounded.

cSCC, cutaneous squamous cell carcinoma; mm, millimetre; n, number.

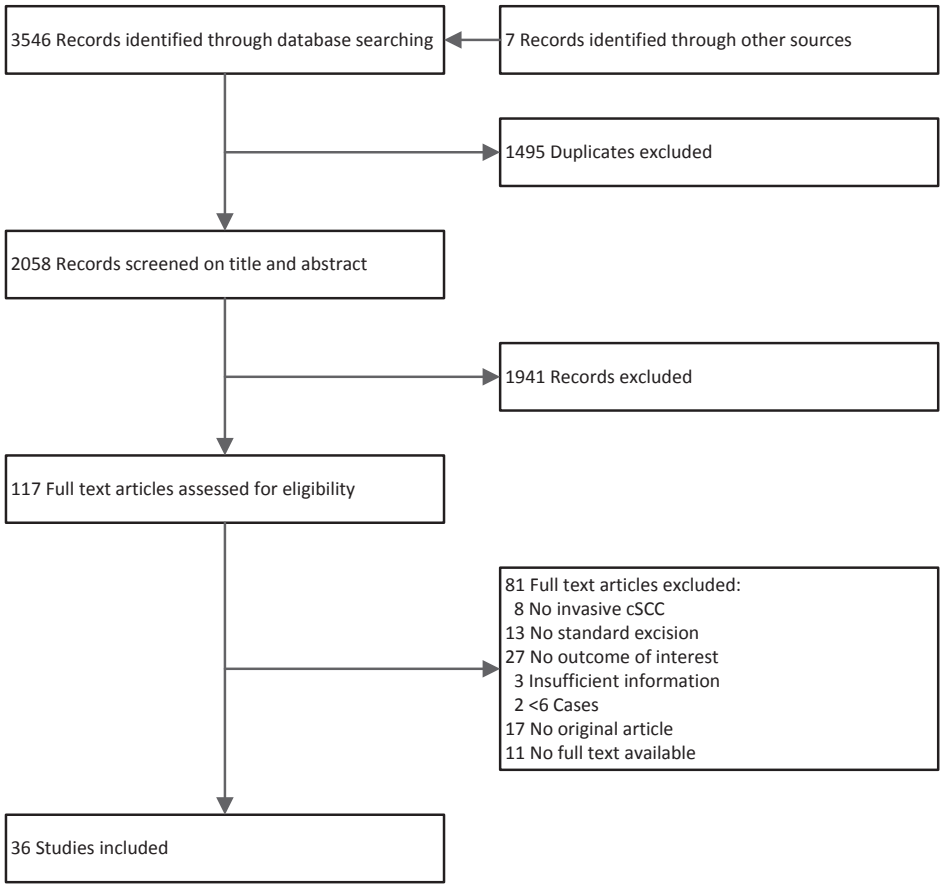


**Figure 1.** Flow-chart of the systematic review.
cSCC, cutaneous squamous cell carcinoma.

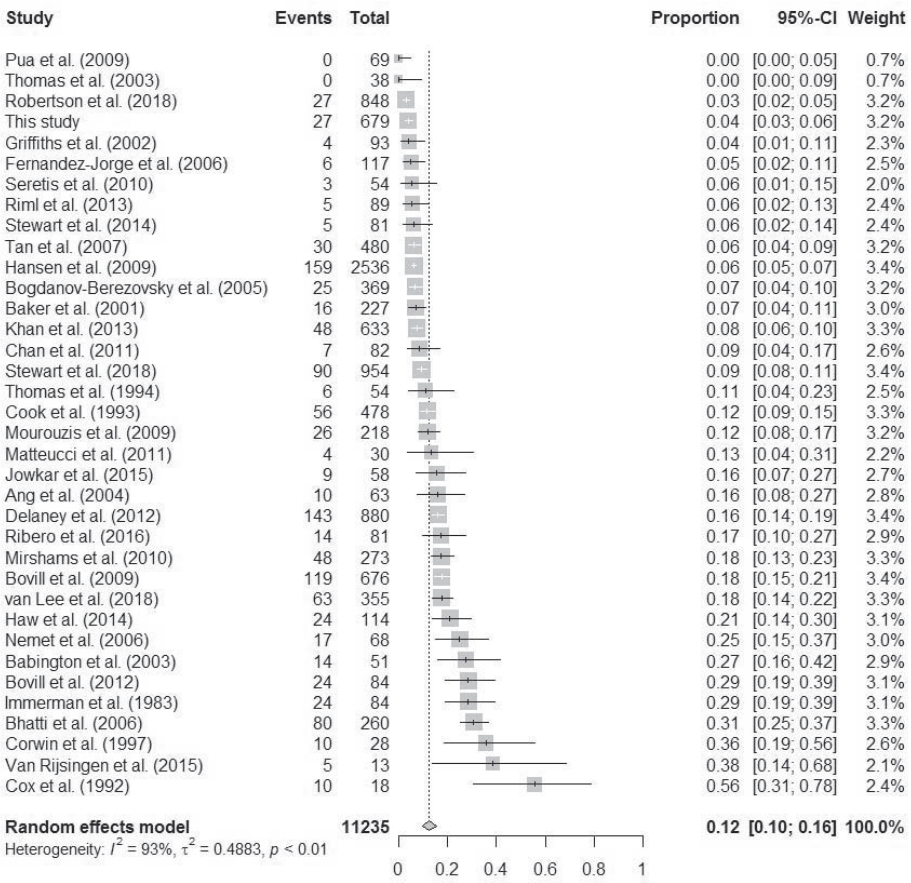


**Figure 2.** Proportions of incompletely excised cutaneous squamous cell carcinoma.
CI, confidence interval.

## DISCUSSION

This prospective observational multicentre study showed that the rate of incompletely excised cSCC was only 4% for a cohort that was dominated by low risk cSCCs while all incompletely excised cSCC were high risk tumours. This indicates that the prescribed excision margin by the Dutch cSCC guideline of five mm for T1 cSCCs is sufficient and that dermatologists are well skilled to clinically demarcate the peripheral margins of cSCCs. The drawback of SE concerns the depth of excision, i.e. incompletely excised cSCCs involved the deep margin in 92%.

Until now, a wide range of incompletely excised cSCC has been reported (range 0%-39%).[11,16-50] This current study shows a lower rate of incompletely excised cSCCs

(4%) than the pooled average estimate of the systematic review (12%, 95% CI 10-16, $I^2$ 92%) whereby the rate of incompletely excised cSCC found in our previous retrospective study was even higher (18%).[11]

The differences in rates of incompletely excised cSCC could be caused by selection bias. First, in our previous retrospective study, MMS was not yet used for cSCCs in the two study centres during the inclusion period of SE. While in this current study, MMS was available during the entire study period (2015-2017) in all six study centres whereby dermatologists and patients might have preferred MMS over SE when cSCCs had high risk features or were clinically hard to demarcate. Secondly, although cSCC location in the H-zone is not indicated as a high risk feature in the AJCC-8, it is suggested that cSCCs in the H-zone might be more often incompletely excised due to deep tumour invasion over the embryonic fusion plates just like it is assumed for basal cell carcinoma (BCC).[15,51] Our previous retrospective study included cSCCs in the head and neck area only, whereby 45% of cSCCs were located in the H-zone, while the majority of the studies in the meta-analysis as well as this current study included all tumour locations. In the current study, only 23% of SCC were located in the H-zone. Thirdly, the recommended excision margins in the Dutch cSCC guideline are wider (i.e. five mm for T1 and ten mm for ≥ T2 cSCC) than in the British, American and Australian guidelines (i.e. four mm for T1 and six mm for for ≥ T2 cSCC).[9,10,52] Fourthly, in this current study all excisions were performed by dermatologists (or residents under supervision of a dermatologist), while for the studies in the meta-analysis the excisions were performed by other specialities than dermatologists in 29 of the 36 studies (i.e plastic surgeons, general surgeons, ophthalmologists, ENT physicians, general practitioners). For BCC, it has been shown that the rate of complete excisions was higher for dermatologist (93%, $p < 0.001$) than for plastic surgeons (83%) and general practitioners (70%).[53] This could also be the case for cSCC as dermatologists are extensively trained and experienced in both BCC and cSCC care compared to plastic surgeons and general practitioners.

Strengths of this study are the prospective multicentre design, the large number of included cSCCs, the detailed information of patient characteristics, cSCC characteristics, histological characteristics and procedural characteristics, and the addition of a systematic review with meta-analysis.

Our study was limited by selection bias because MMS was available in all study centres. The selection bias may be expected to have removed a group of higher risk cSCC. The amount of tumour invasion (mm) was missing in 27% and it was undescribed whether perineural invasion involved nerves lying deeper than the dermis or with a diameter ≥0.1 mm, therefore the numbers of cSCC with stage ≥ T2 were underestimated. Interest-

ingly, in 17% of the SE no cSCC was detected on the histological examination of the excised specimen. For these cases, although exceptionally rare, the cSCC might have been regressed spontaneously or the cSCC was missed by the cuts of the bread loaf technique. Therefore, the truth rate of incompletely excised cSCC might have been underestimated. The follow-up of this study has to clarify if any of these cases recur, which would indicate that they were incompletely excised instead of spontaneously regressed.

It is uncertain if our results can be generalized to other international health care services as the systematic review showed that the efficacy of SE for cSCC differs widely among different subgroups of patients, cSCC, physicians and countries (e.g. due to different recommended excision margins in cSCC guidelines).[5,9,10,52] The systematic review was limited by the retrospective design of the majority of the included studies and poor quality of reporting of the methods and included cases which made them prone to bias. Due to the absence of an applicable scoring tool, the articles included in the meta-analysis could not be scored for quality.

In conclusion, this study showed a low rate of incompletely excised cSCC in a cohort that was dominated by low risk cSCCs, while all incompletely excised cSCC were high risk tumours. This indicates that the prescribed excision margin by the Dutch cSCC guideline of five mm for T1 cSCCs is sufficient and that dermatologists are well skilled to clinically demarcate the peripheral margins of cSCCs. The drawback of SE concerns the depth of excision, i.e. incompletely excised cSCCs involved the deep margin in 92%. Although conclusions about the efficacy of SE must be made carefully as the systematic review showed a wide rate of incompletely excised cSCC. Moreover, the follow-up of this study has to clarify to what extend the efficacy of SE compares to MMS in terms of recurrence rate, metastasis and disease specific death.

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