Clinicopathological Factors Associated with Incomplete Excision of Cutaneous Squamous Cell Carcinoma

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Cutaneous squamous cell carcinoma (SCC) is the second most common type of cancer in Swedish men and women. The incidence of SCC is increasing rapidly. Primary treatment is complete surgical excision with sufficient margins to avoid recurrence and metastasis. The aim of this retrospective study was to identify the clinicopathological factors associated with incomplete excision of SCCs. Clinicopathological data and surgical outcome was obtained for 691 SCCs excised during a 2-year period (2014 to 2015) in Gothenburg, Sweden. Overall, 81 SCCs (11.7%) were incompletely excised. Incomplete excisions were associated with physician specialty and experience, tumour localization in the head and neck region, larger tumour diameter, and lower grade of tumour differentiation. However, multiple regression analysis revealed that large tumour size and excisions carried out by general practitioners were the only factors that significantly negatively affected rates of incomplete excision. These results should be taken into consideration when excising SCCs, in order to avoid multiple excisions.

Key words: squamous cell carcinoma; surgery; incomplete excision; primary care; secondary care.

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Cutaneous squamous cell carcinoma (SCC) is the third most common type of cancer in Sweden, after prostate and breast cancer. It is also the type of malignancy with the most rapidly increasing incidence (1). In 2007, the annual incidence rates for SCC, age-adjusted to the world standard population, were 20.6 per 100,000 population for men and 12.7 per 100,000 population for women, compared with 30.3 and 18.3 per 100,000 population, respectively, in 2017 (2). SCC most commonly develops in chronically sun-exposed areas, resulting in a higher incidence among the elderly population. Fair-skinned, as well as immunosuppressed individuals are also at higher risk (3, 4). Even though the majority of SCCs are low-risk tumours, approximately 2–5% metastasize, most commonly to the lymph nodes (5–7). Primary tumours located on the ear, forehead or scalp also have a higher tendency to metastasize to the parotid gland (7).

SIGNIFICANCE

Cutaneous squamous cell carcinoma is one of the most common skin cancers and its incidence is increasing in many parts of the world, including Sweden. The main treatment is surgical excision with the goal of complete removal, in order to avoid local recurrence as well as metastatic disease. This study found that the 2 most important risk factors for incomplete excision were: excisions carried out by general practitioners and large tumour size. Therefore, general practitioners need further support in managing patients with squamous cell carcinoma, and surgeons should be aware of the difficulties in removing larger tumours.

The primary treatment for SCC is surgical excision with a sufficient margin. Several international and European guidelines, and the national Swedish guidelines recommend excision with 4–10 mm margins measured clinically, depending on the clinical and pathological risk factors of the tumour (8–11). Given the metastatic potential of SCC, it is desirable to completely excise the tumour to avoid recurrence and metastatic disease. In Sweden, several different specialties carry out excisions of SCCs, including dermatologists, plastic surgeons, general surgeons, otorhinolaryngologists, and general practitioners (GPs).

Multiple studies have compared the rates of incomplete excision of SCC in different settings, showing varying rates, ranging from 2.6% to 27.9% (12–24). Several risk factors for incomplete excision have been identified in previous publications, such as tumour location (12, 14, 17, 19, 20, 22, 23, 25), size of the lesion (19, 22, 26, 27), patient sex (18, 19), surgeon experience (18, 20, 24) and physician specialty (13, 15). Nevertheless, these studies reveal conflicting results with regards to the importance of different risk factors. To our knowledge, there is only one smaller Nordic study, including 102 cases, regarding rates of incomplete excision of SCCs and its risk factors (18).

The aim of this study was therefore to evaluate which clinicopathological factors influence surgical outcomes for Scandinavian patients with SCC.

MATERIALS AND METHODS

This retrospective study included all histopathologically verified SCCs that were surgically removed for subsequent examination at the Department of Pathology at Sahlgrenska University Hospital, Gothenburg, Sweden during a 24-month period between 1 January 2014 and 31 December 2015. Only those SCCs excised with the

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Table I. Clinicopathological data collected from electronic patient records and histopathology reports

Category	Data recorded	Recording options
Patients	Sex	Male/female
	Age	Years
Tumour characteristics	Size	Diameter (mm)
	Grade of tumour differentiation	Well/moderate/poor
	Complete excision	Yes/no
	Location	Head and neck/upper extremity/ trunk/lower extremity
Surgical margins	Clinical surgical margin	Maximum distance between clinical tumour border and incision line (mm)
Physician	Specialty	Dermatologist/plastic surgeon/ otorhinolaryngologist/general surgeon/general practitioner
	Experience	Specialist/resident

intention to remove the tumour completely were included. SCCs removed by shave excision, curettage, or partial biopsies were excluded, as were collision tumours. The study was approved by the Regional Ethical Review Board in Gothenburg.

Electronic patient records and histopathological reports were used to compile the clinicopathological data (**Table I**). When full electronic patient records were not available, as was the case for most patients treated within the primary healthcare system, clinical data were retrieved exclusively from the pathology reports. Regarding tumour size, the largest diameter measured on the day of surgery was used. When ambiguous clinical surgical margins were noted (e.g. 3–4 mm), the smallest margin noted on the day of the excision was used. Tumour differentiation, specified by the pathologist, was categorized according to the pathology reports as: well; moderate; poor; or not specified. In cases with a previous diagnostic punch biopsy and conflicting reports on grade of tumour differentiation, the lowest reported grade was chosen. Excisions were considered to be complete when the pathologist reported an absence of invasive tumour cells at the specimen border. Specimens with actinic keratosis or varying degrees of dysplasia, but no invasive tumour remaining at the specimen border were considered to be completely excised.

Statistical analysis

Analyses were conducted using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). Wilcoxon's rank-sum test was used for 2-sample tests. Spearman correlation was used to test for correlations, and multiple logistic regression was used to test incomplete excision vs all significant variables following the unadjusted analysis. p-values <0.05 were considered statistically significant.

RESULTS

In total, 832 surgically treated SCCs were found in the pathology register during the 2-year study period. Among these, 141 lesions were excluded due to: surgery prior to 2014 ($n=35$), treatment by curettage ($n=32$), uncertain diagnosis ($n=26$), partial biopsies ($n=21$), misclassification ($n=16$), collision tumours ($n=8$) and treatment by shave excision ($n=3$). Subsequently, 691 excised SCCs matching the study criteria were included. These tumours were removed from 651 individuals, of whom 270 (41%) were women and 381 (59%) were men. Mean age at diagnosis was 81.1 years (range 47.1–103.7 years) for women and 78.9 years (range 44.1–97.7 years) for men. Mean tumour diameter was 15.8 mm (range 2–100 mm). Most commonly, the tumour was localized in the head and neck region ($n=397$, 57.5%), followed by the upper extremities ($n=164$, 16.6%), the trunk ($n=110$, 15.9%), and the lower extremities ($n=69$, 10.0%). For 2 of the tumours, no information regarding location was available. A preoperative partial biopsy was taken in 240 of 683 SCCs (35.1%) with data available regarding this parameter. The clinicopathological characteristics of the tumours according to the specialty of the physician carrying out the surgery are shown in **Table II**. The parameters affecting the rates of incomplete excision for SCC are listed in **Table III**.

Overall, 81 of the 691 SCCs were incompletely excised (11.7%). Most tumours were excised by dermatologists (47.2%), followed by plastic surgeons (21.9%), otorhinolaryngologists (12.6%), general surgeons (8.7%) and GPs (5.8%). In 27 cases (3.9%), the excision was performed by physicians within other specialties, most commonly ophthalmologists (data not shown). Dermatologists, general surgeons, and otorhinolaryngologists had slightly lower rates of incomplete excision (6.7–12.6%), compared with GPs and plastic surgeons (20.0–20.5%). It was more common for dermatologists, plastic surgeons, and otorhinolaryngologists to excise tumours in the head and neck region (50.6–98.9% of all cases) than for GPs and general surgeons (20.0–25.0%).

The proportions of tumours with moderate to low differentiation excised by dermatologists (38.5%), plastic

Table II. Comparison of tumour characteristics grouped by physician specialty

Specialty	Dermatologist	Plastic surgeon	Otorhinolaryngologist	General surgeon	General practitioner	Other	p-value
Excised tumours, *n* (%)	326 (47.2)	151 (21.9)	87 (12.6)	60 (8.7)	40 (5.8)	27 (3.9)	
Incomplete excisions, *n* (%)	22 (6.7)	31 (20.5)	11 (12.6)	7 (11.7)	8 (20.0)	2 (7.4)	**<0.001**
Body site, *n* (%)							**<0.001**
Head and neck	165 (50.6)	116 (76.8)	86 (98.9)	15 (25.0)	8 (20.0)	7 (25.9)	
Trunk	73 (22.4)	5 (3.3)	1 (1.1)	18 (30.0)	13 (32.5)	0 (0)	
Upper extremities	54 (16.6)	12 (7.9)	0 (0)	17 (28.3)	10 (25.0)	20 (74.1)	
Lower extremities	33 (10.1)	18 (11.9)	0 (0)	9 (15.0)	9 (22.5)	0 (0)	
Unknown	1 (0.3)	0 (0)	0 (0)	1 (1.7)	0 (0)	0 (0)	
Differentiation, *n* (%)							**<0.001**
Well	185 (56.7)	72 (47.7)	41 (47.1)	42 (70.0)	28 (70.0)	15 (55.6)	
Moderate	93 (28.5)	48 (31.8)	34 (39.1)	12 (20.0)	2 (5.0)	8(29.6)	
Poor	23 (7.1)	26 (17.2)	5 (5.7)	3 (5.0)	3 (7.5)	1 (3.7)	
Unspecified	25 (7.7)	5 (3.3)	7 (8.0)	3 (5.0)	7 (17.5)	3 (11.1)	
Tumour size, mm, mean (SD)	13.6 (8.7)	21.1 (12.3)	12.6 (8.0)	17.7 (11.8)	14.8 (19.4)	16.6 (9.5)	**<0.001**

SD: standard deviation. Significant values are shown in bold.

Table III. Clinicopathological parameters and their association with surgical outcome

Clinicopathological category (number of cases with available data)	Clinicopathological parameter	Number of tumours (% of all cases with available data)	Incompletely excised tumours (% of specific parameter)	*p*-value
Body site ($n=689$)	Head and neck	397 (57.6)	60 (15.1)	**0.018**
	Trunk	110 (16.0)	9 (8.2)	
	Upper extremities	113 (16.4)	7 (6.2)	
	Lower extremities	69 (10.0)	5 (7.2)	
Differentiation ($n=641$)	Well	383 (59.8)	37 (9.7)	**0.015**
	Moderate	197 (30.7)	30 (15.2)	
	Poor	61 (9.5)	11 (18.0)	
Tumour size ($n=561$)	<15 mm	364 (64.9)	34 (9.3)	**0.0096**
	>15 mm	197 (35.1)	34 (17.3)	
Specialty ($n=664$)	Dermatologist	326 (49.1)	22 (6.7)	**<0.001**
	Plastic surgeon	151 (22.7)	31 (20.5)	
	Otorhinolaryngologist	87 (13.1)	11 (12.6)	
	General surgeon	60 (9.0)	7 (11.7)	
	General practitioner	40 (6.0)	8 (20.0)	
Physician experience ($n=619$)	Specialist	473 (76.4)	60 (12.7)	**0.034**
	Resident	146 (23.6)	9 (6.2)	
Clinical surgical margins ($n=561$)	<3 mm	8 (1.4)	2 (25)	0.44
	4–6 mm	60 (10.7)	7 (11.7)	
	>6 mm	493 (87.9)	59 (12.0)	

Significant values are shown in bold.

surgeons (50.7%), and otorhinolaryngologists (48.8%) was generally higher than that of GPs (15.2%) and general surgeons (26.3%). Furthermore, plastic surgeons excised tumours of a larger size (mean diameter 21.1 mm) than other specialities (mean diameter 12.6–17.7 mm) as well as a higher percentage of SCCs in the head and neck area. Tumour diameter did not vary between tumours excised by specialists and by residents (mean diameter 15.9 and 15.8 mm, respectively), but specialists excised a larger proportion of lesions in the head and neck region compared with residents (61.1% vs 45.9%, respectively).

The suspected diagnosis prior to surgery was generally made by dermatologists (348 cases, 50.4%) or by GPs (253 cases, 36.6%). SCC was included as a differential diagnosis in the medical patient records or on the pathology referral forms in 74.7% of the cases diagnosed by dermatologists compared with 39.6% of the cases diagnosed by GPs.

Physician-related factors associated with incomplete excision

Physician specialty was important for surgical outcome, with dermatologists having the lowest rates of incomplete excision, whereas GPs and plastic surgeons had the highest rates ($p=0.0004$). The surgeon's level of experience (specialist or resident) was known in 619 cases (89.6%). Among these cases, the majority of SCCs were excised by specialists ($n=473$, 76.4%) and a smaller proportion by residents ($n=146$, 23.6%). Specialists and residents incompletely excised 12.7% and 6.2% of the cases, respectively ($p=0.034$).

Tumour-related factors associated with incomplete excision

Tumour localization was significantly associated with incomplete excision, with head and neck tumours being incompletely excised more often than tumours on the trunk and the extremities ($p=0.018$). Tumours with lower grades of differentiation were also more often incompletely excised ($p=0.015$). When tumours were pooled into 2 groups based on size larger or smaller than 15 mm, incomplete excision was more common in the group of larger tumours ($p=0.0096$). When comparing SCCs without a preoperative biopsy and those with a preoperative biopsy, both groups had the same rates of incomplete excision (11.3%, $p=1$).

Surgery-related factors associated with incomplete excision

Tumours were divided into 3 groups, based on the width of the clinical surgical margins used (<3, 4–6 and >6 mm), but no significant correlation was found between clinical surgical margins and rates of incomplete excision ($p=0.44$). The clinical surgical margin was known in 461 (66.7%) cases. In excisions carried out by GPs, however, the clinical surgical margins were only known in 2 out of 40 cases (5.0%). For all other specialities, the mean clinical surgical margin ranged between 4.2 and 5.4 mm, with standard deviations ranging from 1.21 to 2.06 mm.

Multiple logistic regression was used to test for associations between incomplete excisions and the following variables: physician specialty, tumour size, body site, and grade of differentiation. Physician experience was excluded from the regression analysis due to probable selection bias. Multiple logistic regression showed that tumour size >15 mm ($p=0.035$) and physician specialty ($p=0.035$) were independent factors affecting surgical outcome. With regards to physician specialty, only GPs had significantly higher rates of incomplete excision of SCCs ($p=0.040$) compared with other specialties. Tumour differentiation and tumour site were not independently associated with rates of incomplete excision ($p=0.48$ and $p=0.19$, respectively).

DISCUSSION

In an unadjusted analysis, not accounting for confounding variables, there appear to be multiple factors associated with higher rates of incomplete excision for SCCs, including: tumour localization, tumour diameter, tumour grade of differentiation, physician specialty, and physician experience. However, after adjusting for confounding factors, only 2 risk factors were found to be associated with higher rates of incomplete excision of SCCs: tumour size >15 mm and excisions carried out by GPs. Clinical surgical margins did not correlate with rates of incomplete excision in this study, probably because margins are carefully chosen depending on tumour size, demarcation, body site, and, when available preoperatively, grade of tumour differentiation.

The overall incomplete excision rate was 11.7%, which seems to be relatively comparable to the results of other studies in which the mean overall rates of incomplete excision vary from 2.6% to 27.9% (12–24). Nevertheless, direct comparisons may be difficult, since inclusion and exclusion criteria differ between these studies. In addition, precise definition of what is considered a complete excision is often lacking. Furthermore, many of the published studies focus solely on dermatologists, whereas other studies compare the rates of incomplete excision between different specialties. Some studies also focus on excisions on specific body areas, resulting in higher rates of incomplete excision when only considering more challenging areas, for example.

Several studies have also shown that, the larger the tumour size, the more likely the tumour is to be incompletely excised (22, 26, 27). It has also been suggested that tumours with a diameter greater than 20 mm should be excised with wider margins (27). However, in other studies, no correlation was found between larger tumour size and rates of incomplete excision (12, 23). This may, however, be due to larger tumours being excised with wider margins according to local treatment practise and protocols.

With regards to GPs showing significantly higher rates of incomplete excision compared with surgeons working in secondary care, 2 previous studies have compared the performance of secondary care physicians and GPs. The publication by Haw et al. (15), like ours, revealed that GPs had higher rates of incomplete excision when excising SCCs, compared with dermatologists or other secondary care physicians in eastern and south-eastern Scotland, UK. The incomplete excision rate for GPs in that study was 27.9%, compared with 20.0% in the current study. In contrast, Delaney and co-workers (13) compared the performance of GPs and secondary care specialists in eastern Scotland, and found that GPs performed favourably in excising SCCs compared with secondary care specialists. These differences may be due to differences in local surgical training for GPs in a specific area.

Multiple studies have reported higher rates of incomplete excision for SCCs in the head and neck region, compared with other body sites (12, 14, 17, 19, 20, 22, 23, 25). In the current study, tumours in the head and neck region were more often incompletely excised, compared with tumours on the rest of the body in an unadjusted statistical test, but when confounding factors were taken into account the difference was no longer significant. Other studies also indicate that tumour localization on other body sites, such as lesions on the foot (19), upper extremities (17), genitals, and lower limbs (26), are correlated with higher rates of incomplete excision. Due to the low number of lesions excised on such areas in our study (data not shown), it was inappropriate to proceed with subgroup analyses in the current study.

Previous studies have shown that more experienced surgeons achieve lower rates of incomplete excision compared with surgeons in training (18, 20, 24). However, the current study found a lower rate of incomplete excisions of SCCs among residents. This unexpected result may be due to selection bias, with specialists being assigned more excisions in the head and neck region than residents.

In contrast to the current study, a Danish study by Kjerkegaard & Stolle (18) showed that the use of clinical surgical margins <6 mm in the head and neck area was correlated with higher rates of incomplete excision. Most international guidelines for the management of SCC recommend at least 4-mm margins for low-risk tumours and at least 6-mm margins for high-risk tumours. It is plausible that such recommendations were followed in our study material, thereby minimizing the effects of clinical surgical margins on the rates of incomplete excision. Nevertheless, choosing adequate clinical surgical margins is important to achieve complete tumour resection, which is a key factor to avoid recurrence as well as tumour progression. Therefore, international guidelines should always be followed (8, 9).

When the initial excision is incomplete, re-excision should be performed until margins are histopathologically clear, since patients with incompletely excised SCC have a 4-fold increased relative risk of dying of the disease (28). Incomplete excisions also result in multiple surgeries with increased suffering for the patient and increased costs. With the increasing incidence of SCC in Sweden, the societal costs are also escalating (29), further emphasizing the importance of lower rates of incomplete excision. On the other hand, wide clinical surgical margins may increase the risk of postoperative complications (e.g. haemorrhage, infection or disfiguring scars). Therefore, careful preoperative clinical and dermoscopic tumour demarcation and evaluation of the suspected grade of tumour differentiation is paramount (30, 31).

In Sweden and many other European countries, it is not mandatory for GPs in training to undertake residency in a dermatology department. However, with the increasing incidence of SCC in Sweden, it is of outmost importance for GPs to be able to make a correct diagnosis of SCC and provide adequate treatment or refer the patient to secondary care for surgery (1). Dermatologists should

be encouraged to support GPs to further increase their knowledge in managing patients with SCC.

A potential limitation of this study is that it is a retrospective review of electronic patient records, and not all clinicopathological data could be retrieved. However, this is, to our knowledge, the largest study among the Nordic countries to examine risk factors for incomplete excision of SCC. Another strength of this study is the use of multivariate analysis to take into account confounding factors, and thereby minimize the risk of inaccurate conclusions.

In summary, this study found that the 2 most important factors for incomplete excision of SCC were: large tumour size, and surgery carried out by a GP. This information should be taken into consideration when excising SCCs, in order to achieve the lowest possible rates of incomplete excision and to reduce the risk of metastatic disease, distress for the patient, and the extra costs that multiple excisions entail.

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