DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2023;70(5):A11210852

Non-melanoma skin cancer excision with frozen section histology

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Dan Med J 2023;70(5):A11210852

ABSTRACT

INTRODUCTION. We aimed to determine any risk factors associated with 12-month recurrence and non-radical tumour excision of non-melanoma skin cancer where the tumour has been excised with intraoperative, frozen-section (FS) histopathological assessment; and to examine if FS histopathological assessment may be recomended in certain patient categories.

METHODS. The study was a single-centre retrospective cohort study based on information obtained from patient charts on those treated primarily with FS-aided excision in the 2017-2019 period. A multiple logistic regression model was used to identify risk factors related to non-radical excision.

RESULTS. A total of 655 patients were included; 521 patients presented with basal cell carcinoma (BCC) and 134 patients presented with squamous cell carcinoma (SCC). Superficial, morpheaform and infiltrative BCC subtypes were less likely to be radically excised at first surgical removal than were nodular BCC – most significantly for infiltrative BCC with odds ratio (OR) = 0.48 (95% confidence interval (CI): 0.29-0.77), $p < 0.01$. BCC on the ear was less likely to be excised completely at primary surgery than were tumours in the face, OR = 0.33 (95% CI: 0.16-0.68, p = 0.002). No significant correlation was found for SCC between complete excision and tumour characteristics.

CONCLUSION. Our study suggests that compared with patients with nodular BCC, patients with superficial, morpheaform and especially infiltrative BCC tumours may require FS. Non-radical BCC removal is more frequent on the ear, and FS should generally be considered in this location since delayed re-excision is undesirable.

FUNDING. none.

TRIAL REGISTRATION. not relevant.

Non-melanoma skin cancers (NMSCs) are the most common malignancies in fair-skinned populations. In the US population, NMSC affects approximately 3.5 million people annually [1].

The term NMSC refers to all non-melanoma malignancies of the skin arising from cells within the dermis and epidermis. Basal cell carcinoma (BCC) accounts for approximately 80% of the cases in Western populations [1, 2]. Squamous cell carcinoma (SCC) accounts for approximately 19% of the cases. The last percent is comprised by a wide variety of both carcinomas and sarcomas [3]. Despite an increasing incidence, mortality from NMSC is very low [4]. This is probably owed to both a low metastatic potential of the main tumour types, a greater awareness of cancer in the general population and improved treatment strategies [1, 2].

Numerous treatments for NMSC exist; both surgical and nonsurgical [5]. The non-surgical treatment modalities, including curettage, are beyond the focus of this paper and will not be discussed further.

Surgical treatment includes standard excision of the tumour and application of more precise intraoperative techniques such as Mohs micrographic surgery (MMS), frozen section histology (FS) and other techniques [6, 7]. Studies of these intraoperative methods have been shown to reduce the number of incomplete excisions and the risk of recurrence, especially in high-risk areas [7-9]. The immediate assessment of tumour margins also informs the choice of the best reconstructive method with the least risk of reoperation due to non-radicality.

Performing MMS requires a special surgical training. MMS includes narrow excision of the tumour followed by direct assessment of the specimen. Nearly 100% of the surgical margins are assessed microscopically, and focused re-excision can be performed if any residual tumour is present. The advantages of MMS include high curative rates, narrow excisional margins and low recurrence rates compared with standard surgical treatment. The imitations are the costs, the time aspect, the setup and thorough training in histopathological assessment on the part of the surgeon [10].

Using FS is a well-known alternative to MMS. By this method, the tumour tissue is sent to a pathologist for immediate assessment of tumour margins. FS is also known to have a high curative rate compared with standard surgical excision. Limitations, like MMS, lie in the expensive and time-consuming nature of the procedure. FS does not include complete assessment of the margins why tumour cells may still be present though they were not found in the samples [1]. As a result, subsequent histopathological assessment of the formalin-fixed specimen may reveal residual tumour in the margins. At our department, previous squality assessment has previously shown a false negative rate of 2.6% [11].

Generally, the primary goal for all treatment strategies is complete tumour removal and preservation of a good functional and aesthetic result. In cases in which the tumour borders are difficult to assess macroscopically or reconstructive options are limited, MMS or FS assessment

may be applied with advantage – this is especially indicated in high-risk areas.

As noted, these intraoperative assessments are time consuming and add to the costs of the procedure, why scrutiny of the indication is warranted. The aim of this study was to determine any risk factors associated with 12-month recurrence and risk factors associated with non-radical tumour excision in patients with NMSC where the tumour was excised aided by FS. We aimed to re-evaluate the current indications for FS to optimise quality of treatment, patient safety, satisfaction and cost-effectiveness in the surgical treatment of NMSC.

METHODS

This study was conducted as a single-centre retrospective cohort analysis based on information obtained from patient charts. Assessment for eligibility included all patients who had tumour excision aided by FS at the Department of Plastic and Breast Surgery, Aarhus University Hospital, Denmark, between 2017 and 2019.

The exclusion criteria included patients with cancers other than NMSC, patients who were referred with recurrent NMSC after previous treatment and patients for whom end-point data could not be obtained.

FS was performed at the Department of Pathology to which the entire specimen was sent for assessment. Samples from the margin were taken out by the pathologist during the preperation procedure.

Data recorded from patient charts included gender, age at time of treatment and indication for the use of FS. Furthermore, we recorded data related to the histological diagnosis, tumour characteristics and localisation [12]. Excision margins at primary examination were not obtained since they were not precisely recorded in all patient charts and requiring use of such data would therefore have resulted in exclusion of a vast number of patients. Twelve-month recurrence was recorded based on patient charts and was, in many cases, found during one-year checkup. For the remaining patients, 12-month recurrence was recorded only if they experienced symptoms that led to the diagnosis of cancer recurrence.

Anatomical localisation was categorised into three groups to match previous studies. *High-risk area* was defined as tumours located to the nose, periorbital region, lip and ear. *Non-high-risk area* included tumour locations on the forehead, cheek, chin, temple, scalp and neck. The last anatomical group included tumours on the trunk and extremities.

We applied a multiple logistic regression model to test for statistically significant risk factors for complete tumour removal at primary excision and 12-month recurrence.

Approval for this study (No. 1-45-70-2-21) was obtained from the Legal Office at the Central Denmark Region, Denmark.

Trial registration: not relevant.

RESULTS

A total of 745 patients were screened for the study and 655 were included in the analysis; 521 patients were treated for BCC and 134 for SCC (**Table 1**). Those excluded were mainly patients who had already undergone previous treatment. No basosquamous carcinomas were found within the patient cohort.

All patients except one had a preoperative biopsy confirming the diagnosis of NMSC.

TABLE 1 Basal cell carcinoma and squamous cell carcinoma characteristics.

	BCC	SCC
Gender, % (n)		
Males	51.8 (270)	61.9 (83)
Females	48.2 (251)	38.1 (51)
Age, mean ± SD (range), yrs	69.4 ± 12.7 (24-95)	76.0 ± 11.8 (32-95)
Histological subtype, % (n)		-
Superficial	1.7 (9)	
Nodular	60.8 (317)	
Morpheaform	11.1 (58)	
Micronodular	1.2 (6)	
Infiltrative	25.1 (131)	
Degree of differentiation, % (n)	-	
Well differentiated		8.2 (11)
Moderately differentiated		84.3 (113)
Poorly differentiated		6.7 (9)
Unclassified		0.8 (1)
Localization, % (n)		
High-risk area	76.0 (396)	57.5 (77)
Non-high-risk area	23.8 (124)	39.6 (53)
Trunk and extremities	0.2 (1)	3.0 (4)
Tumour diameter, median (range), mm	9 (3-65)	15 (3-55)
TNM staging, % (n)		
T1	90.4 (471)	62.7 (84)
T2	8.3 (43)	29.1 (39)
T3	0.4 (2)	3.7 (5)
T4	1.0 (5)	4.5 (6)
N0	100.0 (521)	92.5 (124)
N1	0.0	7.5 (10)
M0	100.0 (521)	97.8 (131)
M1	0.0	2.2 (3)
Indication for FS, % (n)		
Flap surgery	0.6 (3)	0.0
Localization	79.1 (412)	15.7 (21)
Histological subtype	18.0 (94)	84.3 (113)
N/A	2.3 (12)	0.0
Complete excision at primary, % (n)[a]		
Yes:	72.2 (376)	76.1 (102)
Superficial	44.4 (4)	
Nodular	79.2 (251)	
Morpheaform	63.8 (37)	
Micronodular	50 (3)	
Infiltrative	61.8 (81)	
No:	27.8 (145)	23.9 (32)
Superficial	55.5 (5)	
Nodular	20.8 (66	
Morpheaform	36.2 (21)	
Micronodular	50 (3)	
Infiltrative	38.2 (50)	
12-mo. recurrent cancer, % (n)		
Yes	4.6 (24)	11.9 (16)
No	93.3 (486)	85.1 (114)
Unknown[b]	2.1 (11)	3.0 (4)

BCC = basal cell carcinoma; FS = frozen section histology; N/A = not applicable; SCC = squamous cell carcinoma; SD = standard deviation; TNM = tumour-node-metastasis.
a) Defined as radically removed tumours at the 1st excision assessed by both FS with free margins and later confirmed by pathological assessment.
b) Lost to follow-up because of death within 12 mos. post-operative, therefore not included in the study.

Basal cell carcinoma and squamous cell carcinoma characteristics

Patients with BCC were generally younger than patients with SCC - mean age 69.4 years compared with 76 years (Table 1). Most excised BCC tumours were of the nodular subtype (60.8%) of which 79.2% were completely excised at primary surgery. SCC tumours were primarily moderately differentiated.

No patients in the BCC population presented with spread to the lymph nodes or distant metastasis, whereas ten patients in the SCC group had lymph node metastasis and another three patients had distant metastases (Table 1).

The main indication for FS was tumour localisation in BCC patients and histological tumour type in SCC patients (Table 1). Among patients, 4.6% of BCC and 11.9% of SCC patients experienced recurrence within 12 months after surgery.

Complete excision of basal cell carcinoma and squamous cell carcinoma

Complete excision at primary surgery was defined as radically removed tumours at the first excision, assessed by FS with free margins and subsequently confirmed by standard pathological assessment. For BCC patients, the rate was 72.2%; for SCC patients, 76%.

We found a statistically significantly lower rate of complete excision at primary surgery for superficial, morpheaform and infiltrative BCC than for nodular BCC . The difference was most significant for infiltrative tumours with odds ratio (OR) = 0.48 (95% confidence interval (CI): 0.29-0.77), $p < 0.01$ (**Table 2**). For tumour localisation, we found that at primary surgery, BCCs on the ears were less likely to be excised completely than were BCCs on the face, OR = 0.33 (95% CI: 0.16-0.68), $p < 0.01$.

TABLE 2 Adjusted odds ratio for complete primary excision of basal cell carcinoma and squamous cell carcinoma.

	Adjusted OR (95% CI)[a]	p value
Basal cell carcinoma		
Histological subtype (n):		
Nodular (317)[b]	-	-
Superficial (9)	0.18 (0.04-0.72)	0.01
Morpheaform (58)	0.48 (0.26-0.89)	0.02
Micronodular (6)	0.21 (0.04-1.12)	0.07
Infiltrative (131)	0.48 (0.29-0.77)	< 0.01
Localization (n):		
Face (110)[b]	-	-
Periorbital (80)	0.81 (0.40-1.66)	0.57
Ear (57)	0.33 (0.16-0.68)	< 0.01
Scalp/neck (14)	0.78 (0.19-3.16)	0.73
Nose (231)	0.82 (0.47-1.43)	0.49
Lip (28)	0.77 (0.29-2.00)	0.59
Tumour stage (n):		
1 (471)[b]	-	-
2 (43)	1.09 (0.51-2.33)	0.82
3[c] (2)	N/A	-
4 (5)	0.10 (0.01-0.94)	0.04
Squamous cell carcinoma		
Degree of differentiation (n):		
Well differentiated (11)[b]	-	-
Moderately differentiated (113)	1.45 (0.31-6.82)	0.64
Poorly differentiated (9)	1.54 (0.16-14.70)	0.71
Unclassified[c] (1)	N/A	-
Localization (n):		
Face (43)[b]	-	-
Periorbital (15)	2.24 (0.49-10.37)	0.30
Ear (21)	2.15 (0.53-8.79)	0.29
Scalp/neck (10)	2.17 (0.36-12.96)	0.39
Nose (16)	1.40 (0.33-6.06)	0.65
Lip (25)	3.88 (0.88-17.02)	0.07
Tumour stage (n):		
1 (84)[b]	-	-
2 (29)	1.29 (0.41-4.12)	0.66
3 (5)	1.54 (0.24-9.85)	0.65
4 (6)	0.44 (0.07-2.67)	0.37

CI = confidence interval; N/A = not applicable; OR = odds ratio.
a) Adjusted for age, gender, histological subtype, tumour localization and tumour stage.
b) Reference value.
c) Not enough observations to perform statistic calculations.

Only T4 BCC tumours had significantly higher odds of being completely excised at primary surgery, OR = 0.10 (95% CI: 0.01-0.94), p = 0.04; probably owed to a wider excisional margin.

No significant correlation vas found for SCC between complete excision and histological subtype, localisation or tumour stage.

SCCs on the lip showed a trend towards being more likely to yield complete primary excision, but the result was only borderline significant, OR = 3.88 (95% CI: 0.88-17.02), p = 0.07.

Twelve-month recurrence in basal cell carcinoma and squamous cell carcinoma

The 12-month recurrence characteristics are presented in **Table 3**. For BCC, location on the nose accounted for half of recurrent cancers. The most recurrent BCC subtype was the infiltrative type (41.7%).

TABLE 3 Twelve-month recurrence in basal cell carcinoma and squamous cell carcinoma.

	BCC, % (n) (N_B = 24)	SCC, % (n) (N_S = 16)
Histological subtype		-
Nodular	29.1 (7)	
Superficial	-[a]	
Morpheaform	25.0 (6)	
Micronodular	4.2 (1)	
Infiltrative	41.7 (10)	
Degree of differentiation	-	
Well differentiated		12.5 (2)
Moderately differentiated		75.0 (12)
Poorly differentiated		12.5 (2)
Unclassified		-[a]
Localization		
Face	20.8 (5)	50.0 (8)
Periorbital	4.2 (1)	12.5 (2)
Ear	12.5 (3)	18.8 (3)
Scalp/neck	8.3 (2)	18.8 (3)
Nose	50.0 (12)	-[a]
Lip	4.2 (1)	-[a]
Tumour stage		
1	79.2 (19)	18.8 (3)
2	16.7 (4)	62.5 (10)
3	4.2 (1)	6.3 (1)
4	-[a]	12.5 (2)
Complete excision primarily[b]		
No	66.7 (16)	50.0 (8)
Yes	33.3 (8)	50.0 (8)
Excisions before complete excision, n[c]		
1	33.3 (8)	43.8 (7)
2	45.8 (11)	56.2 (9)
3	16.7 (4)	-[a]
4	4.2 (1)	-[a]

BCC = basal cell carcinoma; SCC = squamous cell carcinoma.
a) No recurrent cancer reported in the group.
b) Defined as radically removed tumors at the 1st excision assessed by both FS with free margins and later confirmed by pathological assessment.
c) The total number of operations before reaching free margins including initial surgery, every FS and later re-operations if normal pathological assessment showed non-radical removal.

For SCC patients, we observed that 75% of the recurrent cancers were of the moderately differentiated subtype. Half of the recurrent tumours were found in the face.

DISCUSSION

Conventional excision is considered the fastest and least expensive treatment with a curative rate exceeding 95% in low-risk tumours [13]. However, conventional excision with standardised macroscopic excisional margins was shown to result in a higher rate of non-radical primary excision in the facial area, leading to re-excision and a potential risk of local recurrence [14]. Use of intraoperative histological techniques allows the surgeon to narrow down the margins while still performing re-excision before closure or reconstruction in a one-day setting [7, 8].

Reported rates of incomplete excision at primary surgery fall in the 5-25% range for BCC patients and 6.8-17.6% range for SCC patients after standard excision [15, 16]. The present study focusses on incomplete excision at primary surgery with FS. The rather high incomplete excision rates for BCC (27.8%) and SCC (23.9%) were expected since FS is often used to narrow the excisional margins. Furthermore, this selected group of patients by definition has more advanced tumours with uncertain tumour margins.

Non-radical excision was statistically significantly more common on the ears and for T4 tumours. On the ears, the subcutaneous tissue is thin, and the non-radically removed tumours may also be located towards the cartilage. This point is important to consider when assessing the efficacy of FS on the ear.

The fact that higher tumour-stage decreases the odds of achieving complete excision at primary is unsurprising. Furthermore, T4 tumours and the superficial and morpheaform subtypes account only for a few cases why this result should be considered with caution.

Previous reporting on tumour radicality in relation to histological subtype is conflicting [17, 18]. Our findings that nodular BCCs are more likely to be excised with free margins ties in well with the pathological growth pattern for this tumour type. Therefore, application of FS may be more useful in cases with other subtypes since these tumours are more likely to require re-excision.

Our study found no association between SCC tumour characteristics and complete excision at primary surgery; however, for lip tumours, there was a trend towards a higher likelihood of being excised with free margins. Since we had a total of only 134 SCC tumours, the population may be too small to detect significant differences, and we cannot draw any conclusion based on these data. Further studies are warranted to determine if any characteristics in NMCSs are more likely to be completely excised at primary surgery.

For the SCC, we found that 75% of recurrent cancer were of the moderately differentiated group. However, most of our cases were placed in this group and therefore it was not unexpected to see a high rate in this group. A previous study on SCC tumours on the lip found a higher risk of

recurrent cancer although we observed no recurrence in the 25 patients with SCC on the lip [19].

Overall, the dataset is small and retrospective, which entails several limitations. The various estimates that showed no significant association between tumour characteristics and the outcome variables may present differently in a larger study population. Another limitation of our study is the lack of data regarding surgical excision margin measurement. In relation to the small number of recurrent BCC and SCC tumours, we were unable to calculate risk factors associated with 12-month recurrence since the subgroups would only count a few cases each. Therefore, we are unable to conclude if, e.g., histological subtype in SCCs was a risk factor for recurrent cancer.

Generally, only few patients were lost to follow-up, leading to little potential selection bias. Only patients who died within the first 12 post-operative months who were not diagnosed with recurrent cancer at this point were excluded from the study, which minimises the risk of selection bias.

CONCLUSION

Our study suggests that patients with superficial, morpheaform and especially infiltrative BCC tumours may benefit more from the application of FS than patients with nodular BCC since they are less likely to have free margins at the time of their primary surgery, increasing the risk of re-excision. However, if achieving free margins at the time of the primary surgery is of paramount importance, i.e. due to the choice of reconstructive pathway, FS remains relevant though not 100% accurate.

Since non-radical BCC removal is more frequent on the ear, FS should generally be considered there as delayed re-excision is undesirable in this location.

For better quality of treatment, patient safety and satisfaction and to optimise cost-effectiveness, larger, preferably prospective studies are required investigating risk factors associated with complete excision and recurrent cancer for the most common cancer globally.

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Accepted 15 March 2023

Conflicts of interest none. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2023;70(5):A11210852

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