




ORIGINAL ARTICLE HEAD AND NECK

Management of close/positive margins in cutaneous squamous cell carcinoma of the head and neck: a systematised review

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Abstract

Introduction: The authors reviewed close/positive margins in cutaneous squamous cell carcinoma of the head and neck, ensuing recurrence, regional or systemic metastasis, mortality and follow-up management.

Methods: The design was a systematised review from January 2000 to July 2021. The MEDLINE database was searched with 15 articles out of 3104 meeting the inclusion criteria. Pertinent references underpinning the National Comprehensive Cancer Network's Squamous Cell Skin Cancer Guidelines Version 2.2022 were reviewed.

Results: Overall, there were 13,671 cutaneous squamous cell carcinoma lesions. We found pooled rates for positive excision (14.6% at 99% CI [12.97, 16.26]), ensuing recurrence (14.7% at 99% CI [13.51, 15.83]), regional or systemic metastasis (33.8% at 99% CI [33.77, 33.87]), and mortality (46.6% at 99% CI [42.53, 50.65]). Positive excisions most frequently involved the deep margin (73.7%), nose (34.5%) and ear (33.14%). Re-excision of positive margins appeared to confer worse recurrence (35.4%). We found pooled rates for close/positive excision (17% at 99% CI [15.22, 18.84]), ensuing recurrence (17% at 99% CI [15.76, 18.16]), regional or systemic metastasis (30.4% at 99% CI [26.15, 34.73]), and mortality (46.6% at 99% CI [42.53, 50.65]). Mean follow up was 51 months. Surgical re-excision with adequate margins appeared to be most efficacious, followed by radiotherapy. Chemoradiation and chemotherapy appeared less efficacious.

Conclusion: Surgical re-excision with adequate margins remains the gold standard for close/positive margins in cutaneous squamous cell carcinoma of the head and neck, followed by radiotherapy.

Introduction

Epidemiology

Cutaneous squamous cell carcinoma (cSCC) is the world's second most common skin cancer after basal cell carcinoma (BCC).¹ Together they comprise the world's most common malignancies.² Compared to BCC, cSCC is more invasive, metastatic and recurrent post-treatment.³ Each year, around 1.8 million people globally are diagnosed with cSCC;⁴ and approximately 15,000 Americans die from cSCC complications, surpassing 10,000 melanoma deaths.⁵ These figures are estimated due to a relative paucity of data about cSCC management and complications.^{6–8} Concerningly, the global incidence of cSCC jumped 310 per cent between 1990 and 2017, higher than any other malignancy.⁴ Ultraviolet radiation from chronic sun exposure is the top risk factor for developing cSCC,^{9,10} which explains its tendency to appear on the head and neck.^{11,12} Like most skin cancers, cSCC is more common in people with albinism¹³ and Caucasians¹⁴ proximal to the equator.^{15,16}

Other risk factors include chronic wounds,¹⁰ immunosuppression,^{17,18} dermatoses, previous malignancy, actinic keratosis,¹¹ increasing longevity, male sex, smoking^{19,20} and other carcinogens.²¹ Yet, such nuanced variables require further analysis to better understand the 310 per cent incidence leap. For example, should the effect of increasing longevity be teased out from slowing Caucasian population growth and falling smoking rates? Similarly, does enhanced surveillance of elderly skin allow higher reporting of cSCCs that would otherwise be undetected?

Research focus

This paper reviews close/positive margins in cutaneous squamous cell carcinoma of the head and neck (cSCCHN), ensuing recurrence, regional or systemic metastasis, mortality and follow-up management. The aim is to provide clinicians with up-to-date statistical evidence regarding the management of close/positive margins for cSCCHN, hopefully allowing better-informed management plans.

Low-risk versus high-risk cSCC lesions

Low-risk cSCC lesions include well differentiated primary tumours < 2 cm in diameter,^{22,23} especially in the peripheries.²⁴ High-risk features include close/positive margins;⁶ recurrent disease; radial dimensions > 2 cm,²³ depth > 6 mm; invasion of subcutaneous fat, perineural or lymphovascular

structures;¹³ and distant metastasis. High-risk locations include the aesthetically and functionally sensitive regions of the head, such as the anatomical H-zone ('mask area') which overlaps the midface and ears.²¹

Excision margins

Surgical excision with clear radial and deep margins is the mainstay of cSCC management and provides lower rates of recurrence and mortality than close/positive margins.^{6,25,26} Broadly speaking, cSCCHN surgery is divided into standard (traditional) excision and microscopically controlled Mohs surgery. Standard excision is much faster and cheaper to perform than Mohs surgery. However, there is some evidence that the painstaking step-by-step histological analysis during Mohs surgery tends to provide better cosmetic outcomes and preservation of function, and lower rates of recurrence and mortality.^{27,28}

Nevertheless, surgeons can find it difficult to achieve clear margins when seeking to preserve vital aesthetic and functional head and neck components, such as the orbit.¹¹ Thus, it is not uncommon to achieve close or even positive excision margins, which unfortunately are among the worst prognostic factors for a recurrence of cSCC, metastasis and mortality.^{6,18} This is especially true of cSCCHN with deep margins.^{7,26,29–32}

Ideally, a positive (incomplete, involved or surgical failure) margin can be defined as having tumour cells on histopathology.³³ However, it is logical to expand that definition to include a margin of ≤ 1 mm.^{33–35} This is because histopathology techniques such as bread loafing are imperfect and it is not uncommon to find previously unnoticed microscopic cSCC on follow-up histopathology.^{34–36} Further, it can be especially difficult to detect microscopic cSCCHN satellites on deep margins.³⁰ To complicate matters, there is considerable overlap in the literature between positive and close margins. For instance, close cSCC margins range from ≤ 1 mm³⁷ to at least < 5 mm.^{38–40} Therefore, close and positive margins are often grouped as a single entity.^{41–42} This is not surprising given that close margins are often positive on subsequent histopathology³⁵ and higher rates of recurrence are associated with close/positive margins compared to clear margins.³³

In contrast, cSCC clear (negative) excision margins can be deemed free of cSCC on histopathology.⁴³ However, cSCC clear margins are also defined in the literature as ≥ 1 mm,⁴⁴ or ≥ 4 mm,³² or > 5 mm,²³ or > 6 mm,^{13,23} or > 9 mm²³

or ≥ 10 mm.³³ This variability is partly influenced by whether the tumour is considered low or high risk. Indeed, the National Comprehensive Cancer Network (NCCN) guidelines recommend that cSCC lesions < 2 cm in diameter in lower risk regions should be excised with 4 mm margins to ensure a 95 per cent likelihood of non-recurrence.²³ Whereas lower risk lesions > 2 cm should be afforded a 6 mm margin.²³ Yet, in high-risk periorbital and auricular regions, where cSCC is prone to invade subcutaneous tissue, the NCCN recommends a 4 mm margin for tumours < 1 cm, 6 mm for tumours 1–1.9 cm and 9 mm for tumours ≥ 2 cm.²³ Given that the definitions of clear and close margins can overlap, the authors will define a clear margin as free of cSCC on histopathology or at least > 4 mm, a minimalist NCCN definition.

Managing close/positive margins

Surgical re-excision with adequate margins (as noted above) is the gold standard for positive and at-risk close margins in cSCCHN.⁴⁵ Nevertheless, further surgery is not always feasible, as it may unduly endanger critical head and neck structures; or require a complex reconstruction in an otherwise medically unstable patient.⁴⁶ Other multidisciplinary meeting planning considerations include patient preference, the difficulty of attending surgical appointments for immobile elderly patients and futility in distant metastases.

In such cases, radiotherapy (RT) is often preferred, either with curative or palliative intent, depending on multidisciplinary review of patient prognosis.^{13,47} There is also some evidence that adjuvant RT following re-excision may be better than surgery alone.^{48,49} Dosing fractionations for RT vary depending on patient fitness, the size of the cSCC and whether there is regional disease, perineural invasion or lymph node involvement. For example, in an uncomplicated primary tumour of a diameter < 2 cm, the NCCN recommends that radiation oncologists might consider prescribing 30 Gy in five fractions over two to three weeks.²³ In comparison the NCCN recommends that more aggressive cSCC be treated with more intensive and prolonged RT.

Other comparatively less-supported therapies include chemoradiation,^{50–52} chemotherapy,^{6,47,53} cryotherapy^{21,44} and curettage.^{11,54} Immunotherapy shows promise, but its role is still evolving and thus, requires larger randomised controlled trials and reviews to demonstrate its efficacy.^{52,55–57} Logically, sun smart behaviour, such as wearing hats, should accompany any treatment modality.⁵⁸

Methodology

Study selection

MEDLINE was initially searched with multiple search strategies for articles from 1946 to July 2021 (**Figure 1**). Inclusion criteria were meta-analyses, systemic reviews, randomised clinical trials, observational studies, case series, pilot studies or journal articles; management of positive or close excision margins; and studies reporting recurrence, survival, adjuvant therapy and clinical follow-up of at least one year. Further, pertinent references underpinning the NCCN Squamous Cell Skin Cancer Guidelines Version 2.2022 were reviewed.²³ Exclusion criteria included articles published before 2000 and those with less than 10 cSCCHN patients.

Definitions

Per the literature outlined above, the authors adopted these definitions:

1. Excision margins:
 - positive margin is cSCCHN cells on histopathology or a margin ≤ 1 mm
 - close margin is ≤ 1 mm to < 5 mm
 - close/positive margin is an overlapping description of close and positive margins
 - clear margin is free of cSCCHN on histopathology or > 4 mm.
2. Recurrence is regrowth of cSCCHN following an incomplete excision of cSCCHN.
3. Regional or systemic metastasis is cSCCHN extension into regional structures or systemic spread.
4. Mortality is patient death following close/positive margins in cSCCHN.

Results

Article review and inclusion

Overall, 3104 records were screened in MEDLINE (**Figure 1** and **Supplementary material 1**). A further 544 articles underpinning the NCCN guidelines were identified. From both searches, a total of 152 articles were assessed in full text. Of these articles, 15 met the key inclusion criteria. Altogether, 13,671 unique cSCC lesions were identified for inclusion from those 15 studies after the subtraction of otherwise overcounted lesions (**Table 1**). A further 52 background articles were

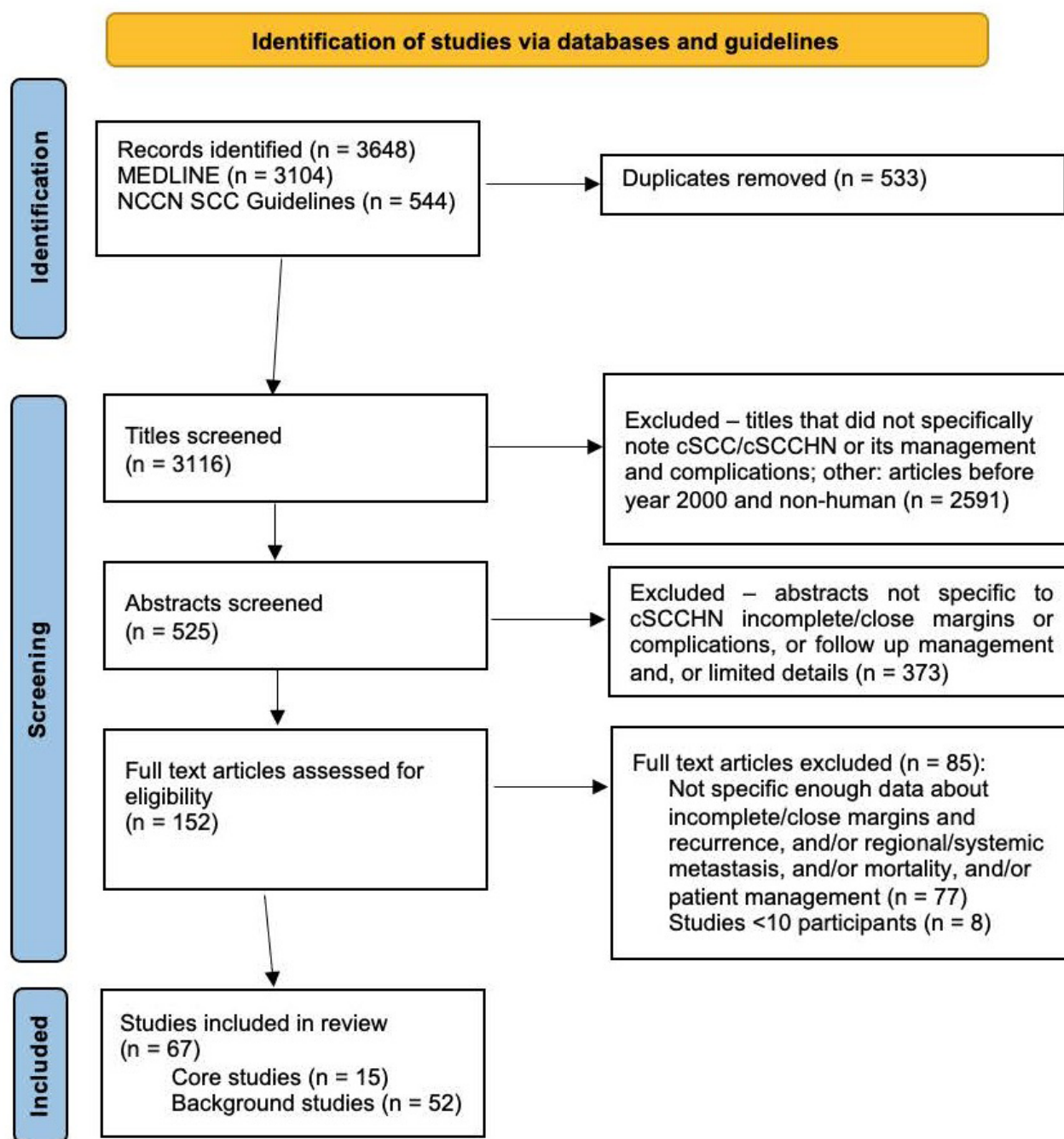


Fig 1. PRISMA diagram showing the process of search, screening, inclusion and exclusion

included which contextualised the core studies.

Patient demographics

The mean age of patients was around 75 and 69.5 per cent of patients were male. Of the 13,671 cSCC lesions identified, 8681 (61.5%) were cSCCHN. Most studies were drawn from predominantly Caucasian populations. The mean follow-up in

the 10 core studies was around 51 months. Patient demographics are summarised in **Table 2**.

Close/positive margins

The close/positive excision rate ranged widely from 6.3 to 76 per cent with a pooled average of 17 per cent at 99 per cent CI [15.22, 18.44] (15 studies). The positive excision rate ranged from 4 to 33 per cent

Table 1. Studies included in the review: cSCC excisions and consequences

Study	cSCC (n)	cSCC excision (%)	Recurrence (%)	Invasion/metastasis (%)	Further treatment	Deaths (%)	Notes
Bovill and colleagues 2009, ⁵⁹ 2012 ⁶⁰	676 (629P)	17.6 (+) 82.4 (-)	5 vs 29 (R) N/A	N/A N/A	Re-excision N/A	N/A N/A	69% of incompletely excised cSCC were cSCCHN
Brinkman and colleagues 2015 ⁴⁴	155 (131P)	33 (+) 67 (-)	N/A N/A	N/A N/A	Re-excision ± RT	~95 ~25	<ul style="list-style-type: none"> 84% of cSCC were cSCCHN While the authors record recurrence, they do not delineate recurrence following positive vs clear excision margins Mortality following positive vs clear margins is approximated from their significant 4.0 RR of dying of cSCC after positive vs clear margins with end of follow-up raw deaths (n = 66)
Overall totals			14	14		50	
Chiller and colleagues 2000 ⁵⁴	849	11.2 (+)	N/A	10–33	Re-excision	N/A	52% of cSCC were cSCCHN
Dalal and colleagues 2018 ⁶¹	138 (138P)	6.5 (+)	N/A	N/A	Wait, re-excision, Adj	N/A	100% of cSCC were cSCCHN (but undifferentiated cf BCC)
Dallari and colleagues 2020 ⁶²	36 (36P)	28 (+) 16.7 (close) 55 (-)	10 0	10 0	Re-excision ± wait Nil	10 0	100% of cSCC were cSCCHN
Genders and colleagues 2020 ³³	10,935	13 (+)	3–5.4	6.7	Re-excision ± RT	N/A	<ul style="list-style-type: none"> ~55.2% of cSCC were cSCCHN Duplicate cSCC lesions already included in our other core studies were not counted
Hasani and Zargarani 2022 ⁶³	118	29.6 (+)	N/A	N/A	Re-excision	N/A	> 95% of cSCC were cSCCHN
Khan and colleagues 2013 ³²	633	7.6 vs ~24 (+)	5.8	2.4	Re-excision ± Adj	N/A	60% of cSCC were cSCCHN
Mirshams and colleagues 2011 ⁶⁴	273	17.58 (+)	N/A	N/A	Re-excision	N/A	<ul style="list-style-type: none"> 73% of incomplete excisions involved the deep margin Incomplete excision: male (15.1%) vs female (27.1%) Most incomplete excisions involved cSCCHN
Phillips and colleagues 2019 ⁶⁵	232 (92P)	59–76 (+/close)	37.6–45.7	17	Re-excision (Mohs)	31.2	<ul style="list-style-type: none"> ~100% of cSCC were SCCHN DFS: overall (68.8%), margin > 5 mm (94.7%)
Rahimi and colleagues 2021 ²¹	521 (232P)	30.3	25	100	Re-excision, imaging	N/A	100% of cSCC were cSCCHN
Tan and colleagues 2007 ²⁸	517 (447P)	6.3 (+)-11.1 (R) -60(R)	5.7–8.1 (est)	5–47	Re-excision ± RT	N/A	~66.7% of cSCC were cSCCHN
Trosman and colleagues 2021 ⁶	104 (104P)	41 (+)	36–47, 62(R)	27	Re-excision + RT	est 15.5–22	100% of cSCC were cSCCHN
Baseline recurrence	66 (63%)		25–53	27.3			
van Lee and colleagues 2019 ⁶⁶	738 (631P)	8.9 (+) 18 (+ Std) 1 (+ Mohs) 92 (-)	7.6–21.2 8–22.2 (Std) 0 (Mohs) 8.1 (Std) 3 (Mohs)	4.5 4.8 0	Re-excision, RT	N/A	<ul style="list-style-type: none"> 100% of cSCC were cSCCHN Follow-up: standard excision—68.4 months (median), Mohs excision—58.8 months (median)

Adj = various non-surgical adjuvant therapies including RT, chemotherapy, immunotherapy; DFS = disease free survival; est = estimated; Invasion/metastasis = locoregional/distant metastasis; Mohs = Mohs surgical excision; N/A = not assessed; P = patients; R = recurrence; RR = relative risk; RT = radiotherapy; Std = standard/conventional excision; (+) = positive margins; (-) = negative margins

Table 2: Studies included in the review: design, demographics and follow-up

Study	Design	Age (years)	Sex (%)	Follow-up
Bovill and colleagues 2009, ⁵⁹ 2012 ⁶⁰	Retrospective	Mean: 75	Male: 61	60 months
Brinkman and colleagues 2015 ⁴⁴	Retrospective	Median: 73	Male: 64.12	81 months (median)
Chiller and colleagues 2000 ⁵⁴	Retrospective case series	Mean: 74.9	Male: 55	N/A but a 3-year study (1997–1999)
Dalal and colleagues 2018 ⁶¹	Retrospective	77% >70	Male: 65	12 months
Dallari and colleagues 2020 ⁶²	Preliminary observational	Median: >75 (overall); 79 (+ve); 81.5 (close)	Male: 83 (+ve); 87.5 (close)	~24 months (+ve); 12–24 months (close)
Genders and colleagues 2020 ³³	Systematic review	N/A	N/A	N/A
Hasani and Zargarani 2022 ⁶³	Retrospective	Mean: 67.9	Male: 70.7	N/A
Khan and colleagues 2013 ³²	Retrospective	Median: 80	Male: 71	N/A, but 24-month study
Mirshams and colleagues 2011 ⁶⁴	Case series	Mean: 63 (+ve); 66.1 (clear)	Male: 81	N/A
Phillips and colleagues 2019 ⁶⁵	Retrospective	Mean: 69	Male: 85	60 months
Rahimi and colleagues 2021 ²¹	Retrospective	Mean: 77.1 (overall); 76 (male); 80.5 (female)	Male: 69.8	≥ 60 months
Tan and colleagues 2007 ²⁸	Prospective observational	Median: 77 Mean: 74.8 (+ve)	Male: 77	N/A, but 2001–2002
Trosman and colleagues 2021 ⁶	Retrospective cohort	Median: 68	Male: 85	24 months (median)
van Lee and colleagues 2019 ⁶⁶	Retrospective	Median: 76	Male: ~69	68.4 months (Std, median) 58.8 months (Mohs, median)

Mohs = Mohs surgical excision; N/A = not assessed; Std = standard or conventional excision; (+ve) = positive margin

with a pooled average of 14.6 per cent at 99 per cent CI [12.97, 16.26] (14 studies). In one study, the rate of positive margins following standard excision was 18 per cent versus 1 per cent for Mohs surgery (van Lee and colleagues).⁶⁶ The positive excision rate of recurrent lesions was 11.1 per cent (Tan and colleagues)²⁸ and 24 per cent (Khan and colleagues).³² Some further details of rates of initial positive margins versus positive re-excision margins are included in **Figure 2**.

Positive re-excision risk details drawn from the studies in **Figure 2** are:

- Khan and colleagues³² recorded a 7.6 per cent positive excision rate for cSCC and around a 24 per cent positive re-excision rate for (recurrent) cSCC.
- Tan and colleagues²⁸ recorded a 6.3 per cent positive excision rate for cSCC and a 60 per cent positive re-excision rate for (recurrent) cSCC.

Anatomical location of margins

The deep margin comprised 73.7 per cent of positive margins at 99 per cent CI [70.85, 76.57] (six studies).^{32,59–62,64} Of positive margins, 34.5 per cent involved the nose at 99 per cent CI [32.54, 36.52] while 33.14 per cent involved the ear at 99 per cent CI [31.15, 35.13] (seven versus eight studies, respectively).^{32,54,59–64}

Recurrence

Recurrence following close/positive or positive margins varied from 4.2–42 per cent.

The pooled recurrence following close/positive margins was 17 per cent at 99 per cent CI [15.76, 18.16] (10 studies) with a mean follow-up of 51.2 months (eight studies). The pooled recurrence following positive margins was 14.7 per cent at 99 per cent CI [13.51, 15.83] (nine studies) with a mean follow-up of 52.3 months (seven studies).

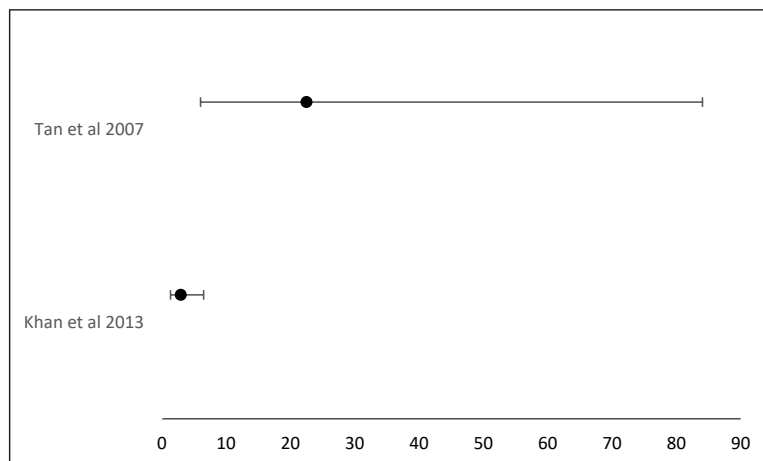


Fig 2. Forest plot 1: positive re-excision risk following initial positive excision

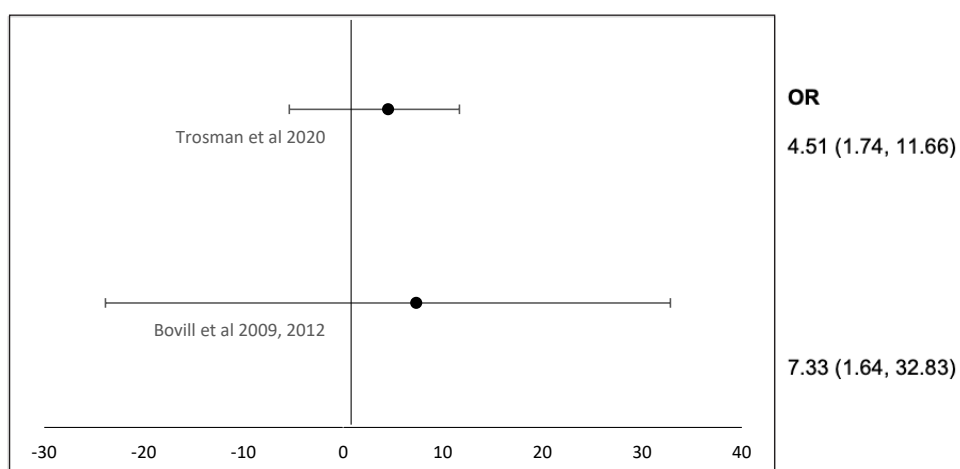


Fig 3. Forest plot 2: recurrence following positive re-excision versus clear re-excision

Recurrence following standard excision versus Mohs surgery was noted in two studies. Genders and colleagues found 5.4 per cent versus 3 per cent (non-significant).³³ Van Lee and colleagues found 3 per cent versus zero per cent (non-significant).⁶⁶

Recurrence after positive re-excision (of margins that were already incompletely excised) varied from 21–62 per cent with a pooled mean of around 35.42 per cent at 99 per cent CI [33, 37.84] (three studies).^{6,59,60,66} Further details are included in **Figure 3**.

Recurrence details drawn from the studies in **Figure 3** are:

- Bovill and colleagues^{59,60} recorded a 5 per cent recurrence following a clear re-excision of an initial positive cSCC excision and a 29 per cent recurrence following a positive re-excision of an initial positive cSCC excision.
- Trosman and colleagues⁶ recorded a 26 per cent recurrence following a clear re-excision of an initial

positive cSCC excision and a 62 per cent recurrence following a positive re-excision of an initial positive cSCC excision.

Regional or systemic metastasis

Regional or systemic metastasis following close/positive or positive margins ranged widely from 2.4 to 100 per cent. The pooled regional or systemic metastasis following close/positive margins was 30.4 per cent at 99 per cent CI [26.15, 34.73] (10 studies) with a mean follow-up of 51 months (seven studies). The pooled regional or systemic metastasis following positive margins was 33.8 per cent at 99 per cent CI [33.77, 33.87] (nine studies) with a mean follow-up of 50 months (six studies). The regional or systemic metastasis for standard excision versus Mohs surgery in one study was 4.5 per cent versus zero per cent (van Lee and colleagues).⁶⁶

Mortality

Mortality following close/positive margins ranged widely from approximately 10 to 95 per cent with a pooled mean of 46.6 per cent at 99 per cent CI [42.53, 50.65] and a mean follow-up of 60.3 months (four studies).

Follow-up management

All 15 studies recommended surgical re-excision as the gold standard for close/positive margins in cSCC. Overall, seven studies recommended RT as an adjuvant or alternative if re-excision was infeasible.^{6,28,32,33,44,61,66} Yet, Rahimi and colleagues found previous RT conferred a 2.0 relative risk (RR) of recurrent cSCC.²¹ They also found no reduced recurrence from adding chemotherapy to radiation. Trosman and colleagues⁶ estimated two-year disease-free survival (DFS) for patients (but not significant) as 71 per cent for surgery alone; 65 per cent for surgery plus radiotherapy; and 58 per cent for surgery and chemoradiotherapy.

Altogether, two studies cautiously recommended watchful waiting be considered in select frail elderly patients.^{62,63} Chiller and colleagues found that pre-excisional curettage reduced cSCC locoregional metastasis (from 33% down to 10%) but did not reduce the risk of positive margins.⁵⁴

Discussion

It is hoped that our up-to-date statistical evidence will help clinicians and patients make better informed choices when faced with close/positive cSCCHN margins. More broadly, we believe that the exponential increase in deadly cSCC requires a greater investment from health departments to arrest this trend.

Patient demographics

This paper reconfirmed that most cSCC patients are elderly, male⁷ and from predominantly Caucasian populations. Preventatively, health departments should consider expanding public health campaigns to better target young fair-skinned males to reduce the rapidly expanding burden of cSCCs on healthcare and society.

Close/positive margins

Our 14.6 per cent positive excision rate is similar to Genders and colleagues 13 per cent.³³ However, their rate was calculated from studies with heterogeneous or missing definitions of positive margins. Similarly, in Rahimi and colleagues, 30.3 per cent of excision margins were ulcerated, which we believe falls under a positive margin.²¹

Yet, they grouped a further 55.9 per cent of excision margins as 'chronic sun damage or precancerous changed cells'. Precancerous cSCC cells are on the cSCC spectrum.²¹ However, chronic sun damage, while cSCC's pre-eminent risk factor,^{9,10} is not cancer. Thus, we conservatively estimated their positive excision rate at 30.3 per cent.

Phillips and colleagues recorded a close/positive margin rate of 76 per cent (0–4 mm).⁶⁵ Perhaps understandably, they wisely refer to the NCCN guidelines to argue for clear margins ≥ 4 –6 mm.

In contrast, Tan and colleagues recommended margins ≥ 5 mm as their 2–5 mm cSCC excision margins yielded a positive excision rate of 6.3 per cent for primary lesions (but 9% for young patients), 11.1 per cent for recurrent lesions and a staggering 60 per cent for re-excision of incompletely excised lesions.²⁸ Similarly, Khan and colleagues³² recorded a positive excision rate of 24 per cent for recurrent lesions. Such findings reinforce the need for adequate margins.

Further, most of our positive excisions involved the deep margin, the nose and ear, which broadly aligned with the literature. The above findings reinforce the need for pursuing clear margins, especially in the H-zone.

Recurrence

Following positive or close/positive excisions, we found a pooled recurrence of 14.7 per cent versus 17 per cent, respectively. However, following a positive re-excision, that figure leapt to 35.4 per cent. Further, there was limited non-significant evidence from two of our studies that Mohs surgery might confer some better outcomes than standard excision, which aligned with some literature.^{23,27} However, there was incomplete detail about the stratification of cSCC tumours and their respective assignment to either standard excision or Mohs surgery. There was also heterogeneous detail about follow-up and comparative histopathology technique. Therefore, further research could better delineate the efficacy of these surgical techniques as well as tumour and patient selection, standard excision histopathology versus Mohs histopathology reliability, and patient follow-up.

Regional or systemic metastasis

The pooled rate of regional or systemic metastasis following positive versus close/positive margins was 33.8 per cent and 30.4 per cent respectively. These very high rates seem to be best explained by our heterogeneous data. For instance, Rahimi and colleagues recorded a close/positive excision

rate of at least 30.3 per cent, but possibly ≥ 80 per cent with an astounding 100 per cent locoregional metastasis of all patients (including clear margins).²¹ They attribute their high rates to specialising in complex and invasive cSCCHN, which would intuitively confer a higher risk.²³

In contrast, Dallari and colleagues' pilot study (follow-up approximately 24 months) recorded only a 10 per cent metastasis rate after 10 positive excisions and no metastases following six close excisions.⁶² However, nine out of ten positive excisions were re-excised with a considerably shorter follow-up than Rahimi and colleagues²¹ (> five years), which might mask otherwise increased rates of metastasis.

Again, when differentiated between standard excision and Mohs surgery, van Lee and colleagues (follow up 63.7 months) found a regional or systemic metastasis rate after positive excision of 4.5 per cent versus zero per cent respectively.⁶⁶ However, this evidence is weak and non-significant given that the zero per cent finding for Mohs surgery was drawn from only three cSCCs that were completely re-excised.

Due to heterogenous data, we grouped regional and systemic metastasis together. Further research might elicit more differences between these categories and related complicated cSCCHN and interventions.

Mortality

Pooled mortality (46.6%) following close/positive margins in cSCCHN is only explored in part by four core articles. For instance, Brinkman and colleagues found a significant 4.0 RR for positive versus clear margins.⁴⁴ While, Phillips and colleagues recorded a 31.2 per cent mortality rate following 59–76 per cent close/positive margins.⁶⁵ These findings might suggest that positive margins confer an increased burden of mortality. However, none of our core studies adequately detail the contribution of patient comorbidities and old age, which intuitively clouds cSCC's precise role in mortality. Indeed, Brinkman and colleagues⁴⁴ conceded that their patients also died of other unstated causes. This paucity of data is reflected in the literature. Therefore, further mortality research is required.

Follow-up management

Our review reconfirmed that surgical re-excision with adequate margins remains the gold standard for managing close/positive margins in cSCCHN. Likewise, surgical excision with adequate margins

is also the gold standard when dealing with an initial presentation of cSCCHN. In either case, the importance of adequate margins cannot be overstated, because of the increased rates of further positive re-excision, recurrence, regional or systemic metastasis, and mortality. This is especially critical when dealing with the deep margin, the nose and ear, which are especially at risk of being found positive. Therefore, we reiterate the wisdom of the NCCN guidelines to pursue clear margins of at least ≥ 4 mm for both initial surgery as well as positive margins.

Further, we found some very limited non-significant evidence in two of our studies that Mohs surgery might be associated with lower rates of complicated cSCCHN. However, as noted earlier, due to incomplete data, further research is needed to better delineate its efficacy versus standard excision. There was also limited evidence in only one older study that pre-excisional curettage may help reduce locoregional metastasis.⁶⁶

Second to surgery, seven studies recommended RT, which should be considered for adjuvant therapy following re-excision or for those unfit for further surgery. However, Trosman and colleagues estimated two-year disease-free survival for surgery alone was better than when RT was added.⁶ On the other hand, Rahimi and colleagues found that previous RT conferred a twofold risk of cSCC recurrence.²¹ Alternatively, it may be that patients with higher risk cSCCHN tend to be selected for RT. Such mixed data supports careful multidisciplinary review when preferencing RT.

Like other studies, this study found that both chemoradiotherapy and chemotherapy were less efficacious than re-excision and RT.

Further, none of our core studies examined immunotherapy specifically. However, our initial literature search yielded some hopeful results. Indeed, in Ferrarotto and colleagues, 20 cSCCHN patients received two cycles of neoadjuvant PD-1 inhibition,⁵⁶ a less morbid modality than re-excision and RT. At 22.6-month follow up, two patients (10%) had recurrence. While such results appear promising, larger immunotherapy trials and reviews are needed in order to facilitate consensus as to its utility.^{52,55–57}

Limitations

Only 61.5 per cent of cSCC lesions were cSCCHN. Our studies were markedly heterogeneous, as reflected in a very wide variation in recurrence and regional or systemic metastasis following close/positive margins. Yet, we were unable to

adequately determine disease specific mortality as mechanisms of death were usually not stated.

Conclusion

This review highlights the need for a standardised definition of positive margins, which are associated with worsened risks of positive re-excision, recurrence and regional or distant metastases. However, disease specific mortality could not be adequately determined. When faced with positive margins in cSCCHN, we recommend re-excision, which remains the gold standard. If surgery is not feasible, we recommend RT. Watchful waiting may be acceptable for select frail or palliative patients.

Conflict of interest

The authors have no conflicts of interest to disclose.

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References

- 1 Fania L, Didona D, Di Pietro FR, Verkhovskaia S, Morese R, Paolino G, Donati M, Ricci F, Coco V, Ricci F, Candi E. Cutaneous squamous cell carcinoma: from pathophysiology to novel therapeutic approaches. *Biomedicines*. 2021;9(2):171. <https://doi.org/10.3390/biomedicines9020171> PMID:33572373 PMCID:PMC7916193
- 2 Bourlidou E, Vahtsevanos K, Kyrgidis A, Tilaveridis I, Patsatsi A, Andreadis D, Cheva A, Patrikidou A, Kitikidou K, Boboridis K. Risk factors for local recurrence of basal cell carcinoma and cutaneous squamous cell carcinoma of the middle third of the face: a 15-year retrospective analysis based on a single centre. *Eur J Dermatol*. 2019;29(5):490–99. <https://doi.org/10.1684/ejd.2019.3643> PMID:31789273
- 3 Lee SY, Hwang WJ, Kim KP, Kim HM, Hwang JH, Kim KS. The relationship between the size and the invasion depth of tumors in head and neck cutaneous squamous cell carcinoma. *Arch Plast Surg*. 2016;43(6):538–43. <https://doi.org/10.5999/aps.2016.43.6.538> PMID:27896185 PMCID:PMC5122543
- 4 Urban K, Mehrmal S, Uppal P, Giese RL, Delost GR. The global burden of skin cancer: a longitudinal analysis from the Global Burden of Disease Study, 1990–2017. *JAAD Int*. 2021;2:98–108. <https://doi.org/10.1016/j.jdin.2020.10.013> PMID:34409358 PMCID:PMC8362234
- 5 Mansouri B, Housewright CD. The Treatment of actinic keratoses—the rule rather than the exception. *JAMA Dermatol*. 2017;153(11):1200. <https://doi.org/10.1001/jamadermatol.2017.3395> PMID:28975200
- 6 Trosman SJ, Zhu A, Nicolli EA, Leibowitz JM, Sargi ZB. High-risk cutaneous squamous cell cancer of the head and neck: risk factors for recurrence and impact of adjuvant treatment. *Laryngoscope*. 2021;131(1):E136–E143. <https://doi.org/10.1002/lary.28564> PMID:32065413.
- 7 Sepehrpour S, Dawood O, Hatter S, Williams L, Zahd Z, Liebmann R, Dheansa B. An assessment of histological margins and recurrence of completely excised cutaneous SCC. *J Plast Reconstr Aest*. 2020;73(5):899–903. <https://doi.org/10.1016/j.bjps.2019.09.022> PMID:32184053
- 8 Givi B, Andersen PE, Diggs BS, Wax MK, Gross ND. Outcome of patients treated surgically for lymph node metastases from cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2011;33(7):999–1004. <https://doi.org/10.1002/hed.21574> PMID:21284049
- 9 Garcia-Zuazaga J, Olbricht SM. Cutaneous squamous cell carcinoma. *Adv Dermatol*. 2008;24:33–57. <https://doi.org/10.1016/j.yadr.2008.09.007> PMID:19256304
- 10 Audet N, Palme CE, Gullane PJ, Gilbert RW, Brown DH, Irish J, Neligan P. Cutaneous metastatic squamous cell carcinoma to the parotid gland: analysis and outcome. *Head Neck*. 2004;26(8):727–32. <https://doi.org/10.1002/hed.20048> PMID:15287040
- 11 Potenza C, Bernardini N, Balduzzi V, Losco L, Mambrin A, Marchesiello A, Tolino E, Zuber S, Skroza N, Proietti I. A review of the literature of surgical and nonsurgical treatments of invasive squamous cells carcinoma. *Biomed Res Int*. 2018;2018:9489163. <https://doi.org/10.1155/2018/9489163> PMID:29808169 PMCID:PMC5902082
- 12 Porceddu SV. Prognostic factors and the role of adjuvant radiation therapy in non-melanoma skin cancer of the head and neck. *Am Soc Clin Oncol Educ Book*. 2015:e513–18. https://doi.org/10.14694/EdBook_AM.2015.35.e513 PMID:25993217
- 13 Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, Dreno B, Fargnoli MC, Forsea AM, Frenard C, Harwood CA. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 1. epidemiology, diagnostics and prevention. *Eur J Cancer*. 2020;128:60–82. <https://doi.org/10.1016/j.ejca.2020.01.007> PMID:32113941
- 14 Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, Peris K, Becker JC, Zalaudek I, Saiag P, Middleton MR, Bastholt L, Testori A, Grob JJ; European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51(14):1989–2007. <https://doi.org/10.1016/j.ejca.2015.06.110> PMID:26219687
- 15 Burton KA, Ashack KA, Khachemoune A. Cutaneous squamous cell carcinoma: a review of high-risk and metastatic disease. *Am J Clin Dermatol*. 2016;17(5):491–508. <https://doi.org/10.1007/s40257-016-0207-3> PMID:27358187
- 16 O'Hara J, Ferlito A, Takes RP, Rinaldo A, Stojan P, Shaha AR, Rodrigo JP, Paleri V. Cutaneous squamous cell carcinoma of the head and neck metastasizing to the parotid gland—a



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- review of current recommendations. *Head & Neck*. 2011;33(12):1789–795. <https://doi.org/10.1002/hed.21583> PMID:22076982
- 17 Manyam BV, Garsa AA, Chin RI, Reddy CA, Gastman B, Thorstad W, Yom SS, Nussenbaum B, Wang SJ, Vidimos AT, Koyfman SA. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. *Cancer*. 2017;123(11):2054–60. <https://doi.org/10.1002/cncr.30601> PMID:28171708
- 18 Bejar C, Basset-Seguín N, Faure F, Fieschi C, Frances C, Guenne C, Lebbe C, Peraldi MN, Roux J, Lamas G, Maubec E; SFORL workgroup. French ENT Society (SFORL) guidelines for the management of immunodeficient patients with head and neck cancer of cutaneous origin. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2014;131(2):121–29. <https://doi.org/10.1016/j.anorl.2014.02.002> PMID:24656876
- 19 Dusingize JC, Olsen CM, Pandeya NP, Subramaniam P, Thompson BS, Neale RE, Green AC, Whiteman DC, for the QSkin Study. Cigarette smoking and the risks of basal cell carcinoma and squamous cell carcinoma. *J Invest Dermatol*. 2017;137(8):1700–708. <https://doi.org/10.1016/j.jid.2017.03.027> PMID:28414022
- 20 De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, Vermeer BJ, Bouwes Bavinck JN, members of the Leiden Skin Cancer Study. Relation between smoking and skin cancer. *J Clin Oncol*. 2001;19(1):231–38. <https://doi.org/10.1200/JCO.2001.19.1.231> PMID:11134217
- 21 Rahimi-Nedjat RK, Tuettenberg A, Sagheb K, Loquai C, Rybczynski B, Grabbe S, Walter C, Al-Nawas B. Factors accelerating recurrences and secondary tumors in cutaneous squamous cell carcinoma. *J Craniomaxillofac Surg*. 2021;49(4):317–22. <https://doi.org/10.1016/j.jcms.2021.02.009> PMID:33608200
- 22 Wermker K, Kluwig J, Schipmann S, Klein M, Schulze HJ, Hallermann C. Prediction score for lymph node metastasis from cutaneous squamous cell carcinoma of the external ear. *Eur J Surg Oncol*. 2015;41(1):128–35. <https://doi.org/10.1016/j.ejso.2014.07.039> PMID:25182221
- 23 National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Squamous Cell Skin Cancer*. Pennsylvania: NCCN. Version 2. 2022.
- 24 Dormand EL, Ridha H, Vesely MJ. Long-term outcome of squamous cell carcinoma of the upper and lower limbs. *J Plast Reconstr Aest*. 2010;63(10):1705–711. <https://doi.org/10.1016/j.bjps.2009.10.003> PMID:19879200
- 25 Pereira CT, Kruger EA, Sayer G, Kim J, Hu J, Miller TA, Rudkin GH. Mohs versus surgical excision in nonmelanoma skin cancers: does location matter? *Ann Plast Surg*. 2013;70(4):432–34. <https://doi.org/10.1097/SAP.0b013e3182834b47> PMID:23486132
- 26 Spyropoulou GA, Pavlidis L, Trakatelli M, Foroglou P, Pagkalos A, Tsimponis A, Lampros E, Delimpaltas A, Demiri E. Cutaneous squamous cell carcinoma with incomplete margins demonstrate higher tumour grade on re-excision. *J Eur Acad Dermatol Venereol*. 2020;34(7):1478–481. <https://doi.org/10.1111/jdv.16167> PMID:31868990
- 27 Seretis K, Thomaidis V, Karpouzis A, Tamiolakis D, Tsamis I. Epidemiology of surgical treatment of nonmelanoma skin cancer of the head and neck in Greece. *Dermatol Surg*. 2010;36(1):15–22. <https://doi.org/10.1111/j.1524-4725.2009.01379.x> PMID:19912277
- 28 Tan PY, Ek E, Su S, Giorlando F, Dieu T. Incomplete excision of squamous cell carcinoma of the skin: a prospective observational study. *Plast Reconstr Surg*. 2007;120(4):910–16. <https://doi.org/10.1097/01.prs.0000277655.89728.9f> PMID:17805118
- 29 Estall V, Allen A, Webb A, Bressel M, McCormack C, Spillane J. Outcomes following management of squamous cell carcinoma of the scalp: a retrospective series of 235 patients treated at the Peter MacCallum Cancer Centre. *Australas J Dermatol*. 2017;58(4):e207–15. <https://doi.org/10.1111/ajd.12520> PMID:27283245
- 30 van Keulen S, Nishio N, Birkeland A, Fakurnejad S, Martin B, Forouzanfar T, Cunanan K, Colevas AD, S van den Berg N, Rosenthal E. The sentinel margin: intraoperative ex vivo specimen mapping using relative fluorescence intensity. *Clin Cancer Res*. 2019;25(15):4656–662. <https://doi.org/10.1158/1078-0432.CCR-19-0319> PMID:31142505 PMCID:PMC7021202
- 31 Dyalram D, Caldron S, Heath J. Margin analysis: cutaneous malignancy of the head and neck. *Oral Maxillofac Surg Clin North Am*. 2017;29(3):341–53. <https://doi.org/10.1016/j.coms.2017.04.001> PMID:28709533
- 32 Khan AA, Potter M, Cubitt JJ, Khoda BJ, Smith J, Wright EH, Scerri G, Crick A, Cassell OC, Budny PG. Guidelines for the excision of cutaneous squamous cell cancers in the United Kingdom: the best cut is the deepest. *J Plast Reconstr Aest*. 2013;66(4):467–71. <https://doi.org/10.1016/j.bjps.2012.12.016> PMID:23352886
- 33 Genders RE, Marsidi N, Michi M, Henny EP, Goeman JJ, Van Kester MS. Incomplete excision of cutaneous squamous cell carcinoma; systematic review of the literature. *Acta Derm Venereol*. 2020;100(3). <https://doi.org/10.2340/00015555-3441> PMID:32128598 PMCID:PMC9128936
- 34 Herruer JM, Taylor SM, MacKay CA, Ubayasiri KM, Lammers D, Kuta V, Bullock MJ, Corsten MJ, Trites JRB, Rigby MH. Intraoperative primary tumor identification and margin assessment in head and neck unknown primary tumors. *Otolaryngol Head Neck Surg*. 2020;162(3):313–18. <https://doi.org/10.1177/0194599819900794> PMID:31987002
- 35 Wee E, Goh MS, Estall V, Tiong A, Webb A, Mitchell C, Murray W, Tran P, McCormack CJ, Henderson M, Hiscutt EL. Retrospective audit of patients referred for further treatment following Mohs surgery for non-melanoma skin cancer. *Australas J Dermatol*. 2018;59(4):302–08. <https://doi.org/10.1111/ajd.12779> PMID:29349770
- 36 Dinnes J, Deeks JJ, Chuchu N, Saleh D, Bayliss SE, Takwoingi Y, Davenport C, Patel L, Matin RN, O'Sullivan C, Patalay R, Williams HC; Cochrane Skin Cancer Diagnostic Test Accuracy Group. Reflectance confocal microscopy for diagnosing keratinocyte skin cancers in adults. *Cochrane Database Syst Rev*. 2018; issue 12:CD013191. <https://doi.org/10.1002/14651858.CD013191> PMID:30521687
- 37 Elliott BM, Douglass BR, McConnell D, Johnson B, Harmston C. Cutaneous squamous cell carcinoma: predictors of positive and close margins and outcomes of re-excision in Northland, New Zealand. *NZ Med J*. 2018;131(1487):23–29. PMID: 30543608.
- 38 Nightingale J, Travers L, Campbell J, Huang J, Green M,

- Warren T, Fitzgerald G. Outpatient surgical management of non-melanoma skin cancers of the head and neck in a regional centre: an analysis of costs and outcomes. *ANZ Journal of Surgery*. 2021;91(1–2):139–44. <https://doi.org/10.1111/ans.16433> PMID:33205533
- 39 Ettl T, El-Gindi A, Hautmann M, Gosau M, Weber F, Rohrmeier C, Gerken M, Müller S, Reichert T, Klingelhöffer C. Positive frozen section margins predict local recurrence in R0-resected squamous cell carcinoma of the head and neck. *Oral Oncol*. 2016;55:17–23. <https://doi.org/10.1016/j.oraloncology.2016.02.012> PMID:27016013
- 40 Matuschek C, Bölke E, Belka C, Ganswindt U, Henke M, Stegmaier P, Bamberg M, Welz S, Debus J, Gioulès A, Voigt A, Volk G, Ohmann C, Wiegelt T, Budach V, Stuschke M, Schipper J, Gerber PA, Budach W. Feasibility of 6-month maintenance cetuximab after adjuvant concurrent chemoradiation plus cetuximab in squamous cell carcinoma of the head and neck. *Strahlenther Onkol*. 2013;189(8):625–31. <https://doi.org/10.1007/s00066-013-0378-2> PMID:23824104
- 41 Guinot JL, Arribas L, Vendrell JB, Santos M, Tortajada MI, Mut A, Cruz J, Mengual JL, Chust ML. Prognostic factors in squamous cell lip carcinoma treated with high-dose-rate brachytherapy. *Head Neck*. 2014;36(12):1737–742. <https://doi.org/10.1002/hed.23529> PMID:24478179
- 42 Goto Y, Kodaira T, Furutani K, Tachibana H, Tomita N, Ito J, Hanai N, Ozawa T, Hirakawa H, Suzuki H, Hasegawa Y. Clinical outcome and patterns of recurrence of head and neck squamous cell carcinoma with a limited field of postoperative radiotherapy. *Jpn J Clin Oncol*. 2013;43(7):719–25. <https://doi.org/10.1093/jjco/hyt066> PMID:23667153
- 43 Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years. *J Am Acad Dermatol*. 2005;53(2):253–60. <https://doi.org/10.1016/j.jaad.2005.02.059> PMID:16021120
- 44 Brinkman JN, Hajder E, van der Holt B, Den Bakker MA, Hovius SE, Mureau MA. The effect of differentiation grade of cutaneous squamous cell carcinoma on excision margins, local recurrence, metastasis, and patient survival: a retrospective follow-up study. *Ann Plast Surg*. 2015;75(3):323–26. <https://doi.org/10.1097/SAP.000000000000110> PMID:24401812
- 45 Leus AJG, Frie M, Haisma MS, Terra JB, Plaat BEC, Steenbakkers RJHM, Halmos GB, Rácz E. Treatment of keratinocyte carcinoma in elderly patients—a review of the current literature. *J Eur Acad Dermatol Venereol*. 2020;34(9):1932–943. <https://doi.org/10.1111/jdv.16268> PMID:32030838 PMCID:PMC7496368
- 46 Szturz P, Vermorken JB. Treatment of elderly patients with squamous cell carcinoma of the head and neck. *Front Oncol*. 2016;6:199. <https://doi.org/10.3389/fonc.2016.00199> PMID:27630826 PMCID:PMC5006317
- 47 Damiani G, Grossi E, Berti E, Conic RRZ, Radhakrishna U, Pacifico A, Bragazzi NL, Piccinno R, Linder D. Artificial neural networks allow response prediction in squamous cell carcinoma of the scalp treated with radiotherapy. *J Eur Acad Dermatol Venereol*. 2020;34(6):1369–373. <https://doi.org/10.1111/jdv.16210> PMID:31968143
- 48 Kampel L, Dorman A, Horowitz G, Fliss DM, Gutfeld O, Muhanna N. Surgically treated advanced cutaneous squamous cell carcinoma of the head and neck: outcome predictors and the role of adjuvant radiation therapy. *Ann Otol Rhinol Laryngol*. 2021;130(9):1016–23. <https://doi.org/10.1177/0003489421990182> PMID:33514267
- 49 Oddone N, Morgan GJ, Palme CE, Perera L, Shannon J, Wong E, Gebiski V, Veness MJ. Metastatic cutaneous squamous cell carcinoma of the head and neck: the immunosuppression, treatment, extranodal spread, and margin status (ITEM) prognostic score to predict outcome and the need to improve survival. *Cancer*. 2009;115(9):1883–891. PMID:19224549
- 50 Tanvetyanon T, Padhya T, McCaffrey J, Kish JA, Deconti RC, Trotti A, Rao NG. Postoperative concurrent chemotherapy and radiotherapy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2015;37(6):840–45. <https://doi.org/10.1002/hed.23684> PMID:24623654
- 51 Giacalone NJ, Qureshi MM, Mak KS, Kirke D, Patel SA, Shah BA, Salama AR, Jalisi S, Truong MT. Adjuvant chemoradiation does not improve survival in elderly patients with high-risk resected head and neck cancer. *Laryngoscope*. 2018;128(4):831–40. <https://doi.org/10.1002/lary.26798> PMID:28833217
- 52 Amoils M, Lee CS, Sunwoo J, Aasi SZ, Hara W, Kim J, Sirjani D, Colevas AD, Chang AL, Divi V. Node-positive cutaneous squamous cell carcinoma of the head and neck: Survival, high-risk features, and adjuvant chemoradiotherapy outcomes. *Head Neck*. 2017;39(5):881–85. <https://doi.org/10.1002/hed.24692> PMID:28252823
- 53 Chabrilac E, Talawdekar A, Garikipati S, Varley I, Sionis S, Beasley N, Jackson R. A single centre's experience of 23 cases of total rhinectomy for the treatment of squamous cell carcinoma involving the nasal vestibule. *Eur Arch Otorhinolaryngol*. 2022;279:2069–75. <https://doi.org/10.1007/s00405-021-06972-6> PMID:34223976
- 54 Chiller K, Passaro D, McCalmont T, Vin-Christian K. Efficacy of curettage before excision in clearing surgical margins of nonmelanoma skin cancer. *Arch Dermatol*. 2000;136(11):1327–332. <https://doi.org/10.1001/arch-derm.136.11.1327> PMID: 11074693.
- 55 Toppi J, Tham YS, Webb A, Henderson MA, Rischin D, Magarey MJR. Surgical management of recurrent cutaneous squamous cell carcinoma of the head and neck after definitive surgery and radiotherapy. *ANZ J Surg*. 2020;90(7–8):1391–395. <https://doi.org/10.1111/ans.16095> PMID:32627359
- 56 Ferrarotto R, Amit M, Nagarajan P, Rubin ML, Yuan Y, Bell D, El-Naggar AK, Johnson JM, Morrison WH, Rosenthal DI, Glisson BS, Johnson FM, Lu C, Mott FE, Esmaeli B, Diaz EM Jr, Gidley PW, Goepfert RP, Lewis CM, Weber RS, Wargo JA, Basu S, Duan F, Yadav SS, Sharma P, Allison JP, Myers JN, Gross ND. Pilot phase II trial of neoadjuvant immunotherapy in locoregionally advanced, resectable cutaneous squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2021;27(16):4557–565. <https://doi.org/10.1158/1078-0432.CCR-21-0585> PMID:34187851 PMCID:PMC8711237
- 57 Tam S, Gross ND. Cutaneous squamous cell carcinoma in immunosuppressed patients. *Curr Oncol Rep*. 2019;21(9):82. <https://doi.org/10.1007/s11912-019-0831-1> PMID:31359288
- 58 Savoye I, Olsen CM, Whiteman DC, Bijon A, Wald L, Dartois L, Clavel-Chapelon F, Boutron-Ruault MC, Kvaskoff M. Patterns of ultraviolet radiation exposure

- and skin cancer risk: the E3N-SunExp Study. *J Epidemiol.* 2018;28(1):27–33. <https://doi.org/10.2188/jea.JE20160166> PMID:29176271 PMCID:PMC5742376
- 59 Bovill ES, Cullen KW, Barrett W, Banwell PE. Clinical and histological findings in re-excision of incompletely excised cutaneous squamous cell carcinoma. *J Plast Reconstr Aes.* 2009;62(4):457–61. <https://doi.org/10.1016/j.bjps.2007.11.041> PMID:18218349
- 60 Bovill ES, Banwell PE. Re-excision of incompletely excised cutaneous squamous cell carcinoma: histological findings influence prognosis. *J Plast Reconstr Aes.* 2012;65(10):1390–905. <https://doi.org/10.1016/j.bjps.2012.04.031> PMID:22652292
- 61 Dalal AJ, Ingham J, Collard B, Merrick G. Review of outcomes of 500 consecutive cases of non-melanoma skin cancer of the head and neck managed in an oral and maxillofacial surgical unit in a District General Hospital. *Br J Oral Maxillofac Surg.* 2018;56(9):805–09. <https://doi.org/10.1016/j.bjoms.2018.08.015> PMID:30219606
- 62 Dallari S, Zaraca G, Giorgini S, Borgonzoni M. Close and positive margins in non-melanoma skin malignancies of the head and neck. What to do in patients over 75 years of age? A preliminary study. *G Ital Dermatol Venereol.* 2020;155(4):464–69. <https://doi.org/10.23736/S0392-0488.18.05853-4> PMID:29963799
- 63 Hasani R, Zargaran M. Frequency of and risk factors for incomplete surgical margins of cutaneous cancers: a retrospective study. *J Dermatolog Treat.* 2022;33(4):2145–148. <https://doi.org/10.1080/09546634.2021.1927948> PMID:34013849
- 64 Mirshams M, Razzaghi M, Noormohammadpour P, Naraghi Z, Kamyab K, Sabouri Rad S. Incidence of incomplete excision in surgically treated cutaneous squamous cell carcinoma and identification of the related risk factors. *Acta Med Iran.* 2011;49(12):806–809. <https://pubmed.ncbi.nlm.nih.gov/22174169/> PMID: 22174169
- 65 Phillips TJ, Harris BN, Moore MG, Farwell DG, Bewley AF. Pathological margins and advanced cutaneous squamous cell carcinoma of the head and neck. *J Otolaryngol Head Neck Surg.* 2019 25;48(1):55. <https://doi.org/10.1186/s40463-019-0374-3>. PMID: 31653276; PMCID: PMC6815033
- 66 van Lee CB, Roorda BM, Wakkee M, Voorham Q, Mooyaart AL, de Vijlder HC, Nijsten T, van den Bos RR. Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs standard excision: a retrospective cohort study. *Br J Dermatol.* 2019;181(2):338–43. <https://doi.org/10.1111/bjd.17188> PMID:30199574