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MR GRANT SWITZER NOLAN (Orcid ID : 0000-0003-0220-3218)

MR JOSHUA P TOTTY (Orcid ID : 0000-0002-0063-1414)

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Incomplete surgical excision of keratinocyte skin cancers: a systematic review and meta-analysis

Running head: Meta-analysis of non-melanoma skin cancer incomplete excision

GS Nolan,[1] AL Kiely,[2] JP Totty,[3] JCR Wormald,[4,5] RG Wade,[6,7] M Arbyn[8] and A Jain[4,9]

1. Department of Plastic and Reconstructive Surgery, Whiston Hospital, St Helens and Knowsley Teaching Hospitals NHS Trust, Warrington Road, Prescot, Merseyside, L35 5DR, United Kingdom
2. Department of Plastic and Reconstructive Surgery, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Trust, Mindelsohn Way, Edgbaston, B15 2TH, United Kingdom
3. Department of Plastic and Reconstructive Surgery, Hull University Teaching Hospitals, Castle Hill Hospital, Castle Road, Cottingham, East Riding of Yorkshire, HU16 5JQ, United Kingdom
4. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Roosevelt Drive, Oxford, OX3 7LD, United Kingdom
5. Department of Plastic Surgery, Stoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust, Aylesbury, Mandeville Rd, Aylesbury HP21 8AL, United Kingdom
6. Leeds Institute for Medical Research, University of Leeds, Leeds, LS2 9JT, United Kingdom
7. Department of Plastic and Reconstructive Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, LS1 3EX, United Kingdom
8. Unit Cancer Epidemiology–Belgian Cancer Centre, Sciensano, Belgium

9. Department of Plastic and Reconstructive Surgery, Charing Cross and St Mary's Hospitals, Imperial College Healthcare NHS Trust, Praed Street, Paddington, London W2 1NY, United Kingdom

Correspondence to: Professor Abhilash Jain
Email: abhilash.jain@nhs.net

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ORCID: GS Nolan - 0000-0003-0220-3218
AL Kiely - 0000-0002-6665-9153
JP Totty - 0000-0002-0063-1414
JCR Wormald - 0000-0001-6197-4093
RG Wade - 0000-0001-8365-6547
M Arbyn - 0000-0001-8434-8263
A Jain - 0000-0002-1799-5310

What is already known about this topic?

- Keratinocyte or non-melanoma skin cancer is the commonest cancer worldwide and current guidelines underestimate incomplete excision rates. These are based on extrapolated data from Mohs micrographic surgery, rather than primary clinical studies.

What does this study add?

- The proportion of incomplete excision was 11·0% for BCCs and 9·4% for SCCs. When based on clinical data the rate is double the proportion suggested by national guidelines. This data suggests that excision by specialists may reduce treatment failure.

Summary

Background

Keratinocyte or non-melanoma skin cancer (NMSC) is the commonest malignancy worldwide. Usual treatment is surgical excision. Current guidelines underestimate incomplete excision rates.

Objectives

We aimed to determine the risk of incomplete excision of NMSCs through a systematic review and meta-analysis of primary clinical studies.

Methods

A PRISMA-compliant systematic review and meta-analysis was performed using methodology proposed by Cochrane. A comprehensive search strategy was applied to MEDLINE, Embase, Scopus, CINAHL, EMCare, Cochrane Library and the grey literature (January 2000–27th November 2019). All studies were included except studies on Mohs micrographic surgery, frozen section or biopsies. Abstract screening and data extraction were performed in duplicate. The risk of bias was assessed using a tool for prevalence/incidence studies. The primary outcome was the proportion of incomplete surgical excisions. A random effects model for pooling of binominal data was used. Differences between proportions were assessed by sub-group meta-analysis and meta regression which were presented as risk ratios. PROSPERO CRD42019157936.

Results

Searching identified 3477 records, with 110 studies included, comprising 53 796 patients with 106 832 basal cell carcinomas (BCC) and 21 569 squamous cell carcinomas (SCC). The proportion of incomplete excisions for BCC was 11·0% (95% CI 9·7-12·4%) and for SCC 9·4% (95% CI 7·6-11·4%). Incomplete excisions by specialty were: dermatology 6·2% BCCs, 4·7% SCCs; plastic surgery 9·4% BCCs, 8·2% SCCs; general practitioners 20·4% BCCs, 19·9% SCCs. The risk of incomplete excision for general practitioners was four times that of dermatologists for both BCC (RR 3·9 [95% CI 2·0-7·3]) and SCC (RR 4·8 [95% CI 1·0-22·8]). Studies were heterogenous (I^2=98%) and at high risk of bias.

Conclusions

The proportion of incomplete excisions is higher than previously reported. Excisions performed by specialists may lower the risk of incomplete excision.

Introduction

Keratinocyte or non-melanoma skin cancer (NMSC) is an umbrella term which includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC) as the most prevalent subtypes. They are the commonest cancers worldwide and in the United Kingdom (UK) they account for 20% of all new malignancies.[1] The UK incidence is 124-148 per 100 000 person years,[2] and is projected to rise due to increased reporting and historic exposure to ultraviolet radiation. In 2020, skin cancer is estimated to cost the NHS over £180 million per annum.[3]

The mainstay of treatment is complete surgical excision. For BCC, the likelihood of recurrence has been well established to be directly related to the adequacy of excision; 1%[4, 5] of BCCs recur where margins are clear, compared to 31-41% recurrence where margins are involved.[6, 7] The same data for SCC is lacking, however given its metastatic potential which is reported at 5-47%,[8] complete excision is desirable. Incomplete excisions may require further surgery or increased surveillance which burdens patients and healthcare systems, increasing the costs and morbidity of skin cancer care.[3]

In the UK, skin cancer excisions are predominantly performed in secondary care.[9] The joint guidance from the National Institute for Health and Care Excellence (NICE) and the British Association of Dermatologists (BAD) includes recommendations regarding surgical margins.[10, 11] Their recommendations are based upon data from studies using Mohs micrographic surgery, which was extrapolated to estimate the expected proportion of incomplete excision with different peripheral margins[12-15] (i.e. 4–5mm peripheral margin is suggested to confer clear margins in 95% of small, well-defined BCCs.)[11] This gave the quoted figure of 5% incomplete excision rate, however this is not based on clinical studies using surgical excision. Two large-scale national audits of BCC and SCC excisions by UK dermatologists have reported different proportions of incomplete excision of between 2.3% to 3%.[16, 17]

The objective of this study was to systematically evaluate observational studies that present the risk of incomplete surgical excision in adults with NMSC worldwide. Secondarily, we aimed to determine if other factors were associated with the risk of incomplete excision.

Materials and methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted in accordance with our peer-reviewed published protocol,[18] registered prospectively on PROSPERO (CRD42019157936) and reported in adherence to Cochrane and PRISMA standards.[19]

Any study reporting the proportion of incomplete excisions for BCCs and SCCs in adult patients (≥ 18 years old) was eligible, regardless of publication status, language or setting. We excluded reviews, case reports, and case series with fewer than 50 patients as these studies may be underpowered to detect incomplete excision rates, and including underpowered studies may reduce the reliability of the meta-analysis. Studies using Mohs micrographic surgery or with intra-operative frozen section were excluded as the margin assessment takes place immediately during these techniques, and wider excisions are performed at the same sitting if tumour extends to a margin. Consequently, the incomplete excision rate for Mohs micrographic and intra-operative frozen section is theoretically close to 0% and including these studies would bias our meta-analysis to a lower proportion of incomplete excision. Furthermore, Mohs micrographic surgery is considered a separate procedure to standard wide local excision by many surgeons and not comparable. Studies reporting lesions expected to have incomplete margins (incision, shave or punch biopsies) were also excluded. Studies reporting on metastatic SCCs, and those located on the perineum and external genitalia (e.g. anal, vulvar and penile SCC) were not included as these patients are often treated via a different pathway to cutaneous lesions and require different management.

In accordance with our published protocol,[18] a structured search of MEDLINE, Embase, Scopus, CINAHL, EMCare, and Cochrane Library was undertaken from January 2000 onwards. The search was performed on 27th November 2019 however several more recent publications were identified after the search through hand-searching of included references and included. We limited studies to those conducted post-2000 as skin cancer care has progressed over time and data more than 20 years old is unlikely to be representative of current clinical practice. Additionally, the grey literature was searched using Open Grey, dissertation databases (e.g. Open

Access Theses and Dissertations) and clinical trial registries (e.g. World Health Organization International Clinical Trials Registry Platform). We hand-searched the reference lists of included studies, relevant reviews, national clinical practice guidelines, and other relevant documents to identify cited articles not captured by electronic searches. Two authors (GSN, ALK or JPT) independently dual screened all titles and abstracts and obtained full text for references potentially meeting the inclusion criteria in Rayyan.[20] Translations were obtained for non-English articles using Google translate. The final decision about inclusion was based on the full texts. Discrepancies between reviewers were resolved through discussion.

Data analysis

Data were independently extracted onto a bespoke electronic sheet by two authors (GSN, ALK or JPT). Data on study demographics and design, patient demographics, time period of study, and risk of bias were collected. The primary outcome was the proportion of incomplete excisions (defined as residual tumour at either the peripheral or deep margin on histological examination). 'Closely' or 'near to' excised lesions were considered as completely excised. Secondary outcomes were other factors which might be related to the risk of incomplete excision such as the discipline of the operating surgeon, the location of lesions, the types of reconstruction performed (e.g. skin grafts and flaps), the histological components,[10, 21] the use of loupe magnification, and year of study publication. Eleven study authors were contacted about missing data and responses were received from seven.

The risk of bias was assessed twice and independently by three authors (GSN, ALK and JPT) using a risk of bias tool for studies of prevalence/incidence.[22] This comprises of signalling questions and a summary assessment, which assesses the external validity of the study (selection and non-response bias) and the internal validity (measurement bias and bias related to analysis). Responses for individual items were either high or low risk of bias, and if there was insufficient data to decide the default was high risk of bias. The summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgement, given responses to the preceding questions, which is in line with Cochrane approaches.[23, 24] Response options for the summary assessment were low, moderate, or high risk of bias.

The pooled proportion of incomplete surgical excision of BCCs and SCCs were estimated using the *metaprop* package[25] in Stata/MP v15 (StataCorp). Dersimonian and Laird random-effects were used given the clinical heterogeneity. The Freeman-Tukey arcsine transformation was used to stabilise the variance. 95% confidence intervals (CI) around the study-specific and pooled proportion were computed using the score-test statistic.[26] Variations in the logit of the proportion of incomplete excisions by operator, use of loupes, year of publication, study design and the overall risk of bias were further explored by subgroup meta-analyses and meta-regression using the *metareg* procedure.[27] The results of the meta-regressions were back transformed and are presented as risk ratios (RR). To account for the inflated type 1 error rates associated with meta-regression in the presence of many covariates and heterogeneity, p-values were corrected using the Monte Carlo permutation test with 20,000 iterations.[28] Three sensitivity analysis were undertaken. Firstly, where studies judged to be at high risk of bias, secondly when conference abstracts were excluded (as the limited word count of this format prevents proper methodological assessment of the study) and finally if study design (prospective/retrospective) affected the risk of incomplete excision. Further subgroup analyses of pooled NMSC (all BCCs and SCCs) were undertaken to address the secondary objectives as reconstruction of a defect is not specific to a type of skin cancer and lesions with a preclinical diagnosis of BCC or SCC are often found to be histologically different. We explored the proportion of incomplete excision by the overall risk of bias (high, moderate or low), study design (prospective vs. retrospective), the method of reconstruction, the proportion of lesions on the head and neck, use of loupes and year of study publication. Statistical heterogeneity was assessed by I^2 which corresponds with the proportion of total variation due to inter-study heterogeneity and by p-values for inter-study heterogeneity and overall.[29] A z-test (and the corresponding p-values) assessed whether the observed proportion was different from zero percent.

In order to assess possible small-study effects (or publication bias across studies), we produced a funnel plot using *metafunnel*.

Differences from the protocol

To accurately estimate the proportion of incomplete excision, we used the Freeman-Tukey arcsine transformation, rather than logit transformation, to stabilise the variances of proportions close to zero.

Data on histological components could not be extracted due to only a subsection of criteria being reported or was not reported for the majority of studies.

Results

Of the 3477 citations identified by the search strategy, 110 studies[16, 30-138] met the inclusion criteria (Figure 1). The characteristics of included studies are summarised in Table 1 and detailed in Supplementary Table 2.

A total of 106 832 BCC and 21 569 SCC excisions were included. These were excised from 53 796 patients across all studies (25 studies did not report the number of patients, instead reporting the number of lesions only).[16, 17, 34, 49, 59, 60, 62, 68, 69, 71-74, 78, 82, 96, 104, 107, 109, 112, 115, 120, 133, 135, 136] The mean age of patients undergoing BCC excision was 67·4 years (SD 14.9) and for SCC excision was 70·9 years (SD 14·1). Most patients were male (BCC 55·7% and SCC 65·1%).

Serious bias was present in the data, especially selection bias which might have been due to the retrospective design of the majority (82%) of studies. Selection bias was primarily due to the exclusion of lesions at higher risk of incomplete excision (e.g. previously incomplete) and including only a subset of patients (e.g. using Mohs micrographic surgery for more challenging cases). A minority of studies included consecutive excisions. Many studies did not include sufficient information on why participants were excluded. A definition and/or statement that lesions were examined by a histopathologist were absent in 38% and 28% of studies, respectively although It is very unlikely that studies from the last 20 years are not reported by a histopathologist. Errors and inconsistencies were identified in 12% of studies in either the numerator, denominator or differing figures throughout the text. Studies which were reported as conference abstracts only were often judged to be at a higher risk of bias than full papers. The risk of bias summary plot is shown in Figure 2. The individual risk of bias for each study is included in the Supplementary Figure 1.

The total proportion of incomplete excisions for BCCs was 11·0% (95% CI 9·7-12·4%) and for SCCs was 9·4% (7·6-11·4%). When analysed by the operating specialty, dermatology had the lowest proportion of incomplete excisions and general practitioners had the highest (Figure 3 and 4, study-level estimates in Supplementary Figures 2-7.) Meta-regression showed that general practitioners were more likely to incompletely excise BCCs than dermatologists (RR 3·9 [95% CI

2·0-7·3] p<0·001, permuted p=0·002) and plastic surgeons (RR 2·4 [95% CI 1·4-4·2] p=0·003, permuted p=<0·001). Similarly, general practitioners had a higher proportion of incomplete SCC excisions than dermatologists (RR 4·8 [95% CI 1·0-22·8] p=0·05, permuted p<0·001) and plastic surgeons (RR 2·2 [95% CI 1·2-8·5] p=0·021, permuted p=0·002). Dermatologists had a lower proportion of incomplete excisions than plastic surgeons for both BCCs (RR 0·4 [95% CI 0·2-0·7] p=0·003, permuted p<0·001) and SCC (RR 0·3 [95% CI 0·1-0·8] p=0·021, permuted p=0·002).

Table 2 shows that plastic surgeons performed more complex reconstructions (skin grafts and flaps) than dermatologist for all NMSC. Other surgeons, such as maxillofacial surgeons and ophthalmologists, performed a similar proportion of reconstructions. No studies on excisions by general practitioners reported how the defects were reconstructed. Plastic surgeons excised a larger proportion of lesions from the head and neck compared to dermatologists, who in turn excised a higher proportion than general practitioners.

Intraoperative use of loupes was not associated with a different incomplete excision risk for NMSC (RR 1.6 [95% CI 0·3-7·4] p=0·537; Supplementary Figure 8). Over 20 years, there was no change in the proportion of incomplete excision NMSC (p=0·904; Supplementary Figure 9).

There was substantial statistical heterogeneity both within and between groups.

Sensitivity analysis using studies at low overall risk of bias only yielded a very similar proportion of incomplete excision of NMSC (10·2% [95% CI 8·5-12·1]; Supplementary Figure 10). The proportion of incomplete excisions for NMSC was similar between full papers, abstractions or conference materials (RR 1·0 [95% CI 0·7-1·5] p=0.826). Prospective studies reported a lower proportion of incomplete excision than others (RR 0·6 [95% CI 0·4-0·9] p=0.034; Supplementary Figure 11).

A funnel plot for all studies showed that datapoints are widely dispersed and the scatter is asymmetrical (Supplementary Figure 12; Egger's regression co-efficient 2·26 [95% CI 2·04-2·48] p<0·001) which suggests the presence of small-study effects.

Discussion

On the basis of 110 clinical studies, we have shown that the proportion of incomplete excisions for BCCs is 11·0% and SCCs is 9·4%. There is substantial variation and heterogeneity in the observed proportion of incomplete excision, ranging from 4·7 – 20·4% by operator. Dermatologists had the lowest proportion of incomplete excisions (6·2% BCCs, 4·7% SCCs) and general practitioners had the highest proportion (20·4% BCCs, 19·9% SCCs). Plastic surgeons had a slightly higher proportion of incomplete excisions than dermatologists (9·4% BCCs, 8·2% SCCs) however a greater proportion of their lesions were located on the head and neck (92·7%), and they also performed more complex reconstructions such as skin grafts and flaps, which imply that the lesions were likely to be larger or the macroscopic margin was less well defined. The use of loupe magnification had no statistically significant effect on the risk of incomplete excisions. Our risk estimates for incomplete excision of NMSCs are the most comprehensive to-date and should be used to inform the design of future studies and in the consent process for patients worldwide.

This study is limited by the high risk of bias in the majority of studies. More than 1 in 10 studies excluded recurrent, previously incomplete and other high-risk lesions from their primary studies. Further selection bias through the differential use of Mohs micrographic surgery by specialty and country will remove lesions that are at the highest risk of incomplete excision. Finally, standard histology using 'bread-loaf' techniques only assesses between 0.19% - 2% of specimen margins[139-141] so consequently, the actual incomplete excision rate in the population is likely to be higher than our estimates suggest. Prospective studies were found to be at a lower risk of incomplete excision than retrospective studies, which may be due to selection bias caused by stricter inclusion criteria of randomised controlled trials than retrospective studies. Evidence of publication bias was identified by asymmetry in the funnel plot which is another limitation. Whilst there was statistically significant heterogeneity amongst studies, the greatest strength of this study is the breadth of data synthesised and readers should consider whether this heterogeneity is clinically relevant. A recent systematic review of incomplete SCC excisions showed a similar finding to ours (13%)[142] but included metastatic disease and fewer cases.

Our forest plots and meta-regression identify large differences in the proportion of incomplete excisions by different operating groups (Figures 3 and 4). General practitioners are four times as likely to incompletely excise NMSC compared to dermatologists (BCC OR 3·9 [95% CI 2·0-7·3], SCC OR 4·8 [95% CI 1·0-22·8]). This finding cannot be explained by selection bias, as it seems unlikely that general practitioners are excising more complex lesions than those they refer to dermatologists. Our data supports the notion that excisions of NMSCs should not be undertaken by non-specialists, as they may lack sufficient training and support which translates into a higher rate of incomplete excision. Multiple studies have shown that general practitioners with a special interest in skin cancer were at a lower risk of incomplete excision than their colleagues,[78, 125] so we see no reason to restrict excisions to secondary care. It is worth noting that a low risk, truncal BCC in an elderly patient that has been incompletely excised may never clinically recur, and incomplete excision does not always necessitate further surgery. The low risk for dermatologists is likely multi-factorial. The prevalent use of Mohs micrographic surgery by dermatologists is effective at removing the highest risk lesions from their caseload, and accordingly they typically excise a greater volume of smaller, lower risk lesions. The more complex lesions they encounter are referred to plastic surgeons (27-52%[101, 143, 144] of skin cancer referrals plastic surgeons receive are from dermatologists). In contrast plastic surgeons excised larger lesions, of more aggressive subtypes, with indistinct macroscopic borders, and this study accordingly found a higher proportion of incomplete excision of BCCs (9·4%) and SCCs (8·2%). This systematic review highlights that the current skin cancer pathways are effective, with dermatologists excising large numbers of low risk lesions whilst plastic, ophthalmological, and head & neck surgeons deal with more difficult lesions which may also require reconstruction.

Specific anatomical factors also likely play a large role in the risk of incomplete excision. Periocular lesions appeared to be at a greater risk as shown by the relatively high risk with ophthalmology and plastic surgery studies on this subset of patients.[67, 87] Additionally, high-risk histological lesions, such as morphoeic BCCs, have been shown to be at higher risk of incomplete excision. In this systematic review, due to a lack of reporting of some high-risk elements such as peri-neural invasion, it was not possible to extract data on histological factors. Two studies were solely on morphoeic BCCs and these reported very different proportions of incomplete excisions

of 6%[120] and 32%.[65] Additionally other factors may impact the proportion of incomplete excision which were not explored by this systematic review, such as the grade of the operating surgeon, the margin of normal tissue taken and the apriori plan for reconstruction: if the surgeon plans to close directly then this may bias the excision towards a smaller margin, whereas when a surgeon plans to reconstruct a defect with a skin graft then comparably a more liberal margin may be taken. These factors would be best explored using Bayesian techniques. With SCC the margin used in different studies was infrequently reported in the larger studies.[17, 42, 59, 78, 107, 115, 125, 129] When it was reported, several studies found no association between wider margins and reduced proportion of incomplete excision,[92, 130] often as the deep margin was primarily affected.[92]

Audits of outcomes following NMSC excisions will undoubtedly continue throughout plastic surgery and dermatology units worldwide, of which the majority will never be published. Future published studies must be of higher methodological quality and should be prospective and include consecutive excisions as a minimum. Multi-centre, national, annual audits such as those performed by UK dermatologists[16, 17] provide the most useful data and other specialties and countries should follow suit. Our study has demonstrated the proportion of incomplete excision is substantially higher than previously reported. In light of these findings, guidelines should be updated, and action taken to improve the outcomes of the world's commonest malignancy.

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Data statement:

The extracted data are freely available via the Open Science Framework (https://osf.io/6znhb/) and the statistical syntax can be obtained from RGW/MA.

Figure legends

Figure 1: PRISMA flow diagram. (Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097)

Figure 2: Risk of bias summary graph for included studies. Risk of bias was assessed using a tool specifically designed for observational prevalence/incidence studies.[22]

Figure 3: A forest plot of the summary estimates of the risk of incomplete excision for basal cell carcinomas (BCCs) split by specialty. General practitioners were more likely to incompletely

excise BCCs than dermatologists (RR 3·9 [2·0-7·3] p<0·001, permuted p=0·002) and plastic surgeons (RR 2·4 [1·4-4·2] p=0·003, permuted p=<0·001). Dermatologists had a lower risk of incomplete excision than plastic surgeons (RR 0·4 [0·2-0·7] p=0·003, permuted p<0·001).

Figure 4: A forest plot of the summary estimates of the risk of incomplete excision for squamous cell carcinomas (SCCs) split by specialty. General practitioners were more likely to incompletely excise SCCs than dermatologists (RR 4·8 [1·0-22·8] p=0·05, permuted p<0·001) and plastic surgeons (RR 2·2 [1·2-8·5] p=0·021, permuted p=0·002). Dermatologists had a lower risk of incomplete excision than plastic surgeons (RR 0·3 [0·1-0·8] p=0·021, permuted p=0·002).

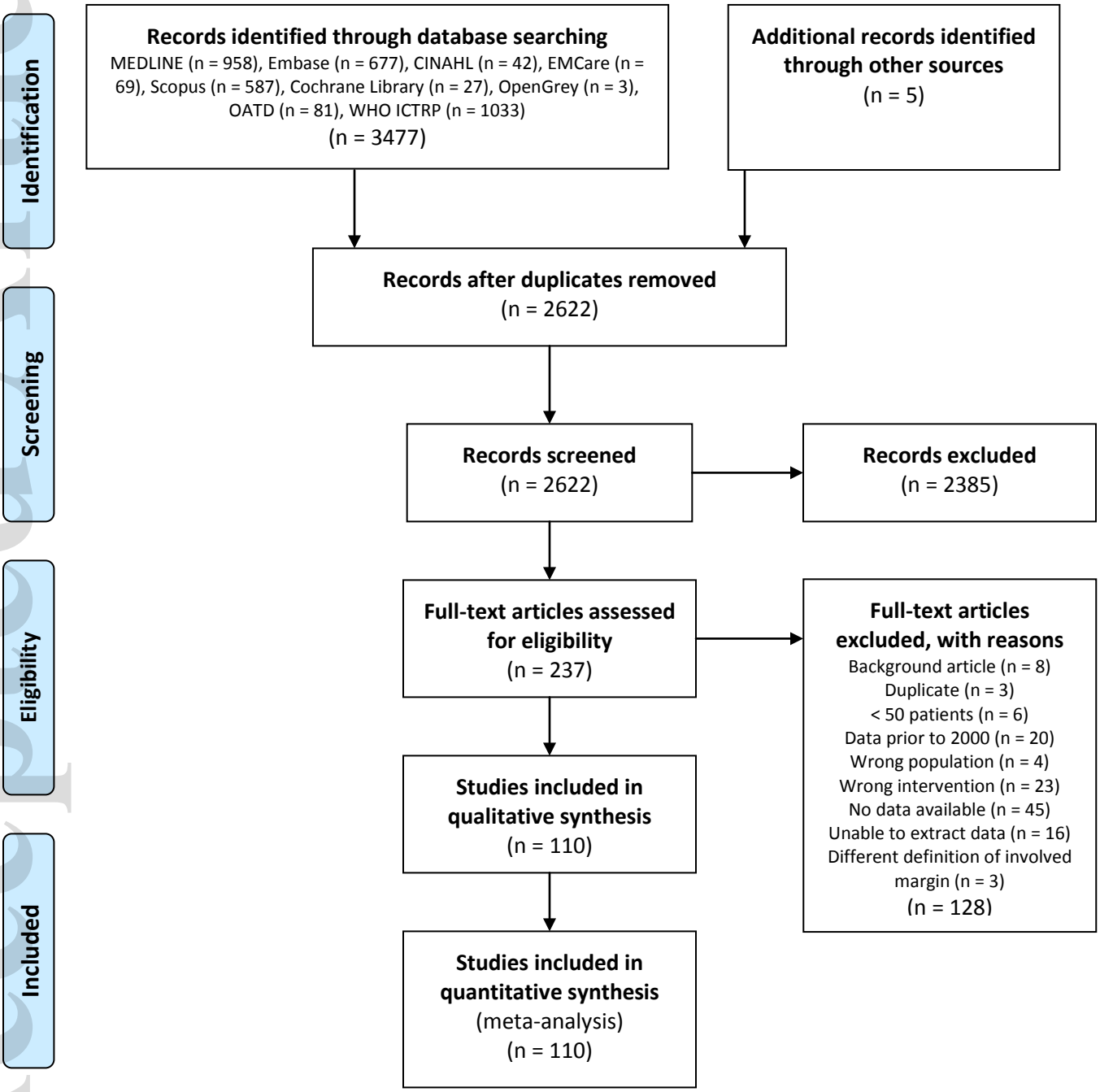
CHARACTERISTIC			NUMBER OF STUDIES	PERCENTAGE OF ALL STUDIES
STUDY DESIGN	Randomised controlled trial		3	3%
	Cohort	Prospective	10	9%
		Retrospective	47	43%
		Other	7	6%
	Case-series	Prospective	6	6%
		Retrospective	33	30%
		Other	4	4%
YEAR OF PUBLICATION	2000 – 2005		5	5%
	2006 – 2010		31	28%
	2011 – 2015		49	45%
	2016 – 2019		25	23%
COUNTRY OF ORIGIN	Europe		69	63%
	Asia		19	17%
	Oceania		14	13%
	South America		7	6%
	North America		1	1%
SPECIALTY	Plastic surgery		37	34%
	Dermatology		22	20%
	Maxillofacial surgery		10	9%
	General practice		8	7%
	Ophthalmology		4	4%
	Ear, nose & throat surgery		1	1%
	Other		28	26%
TYPE OF PUBLICATION	Full paper		79	72%
	Conference abstractions		28	26%
	Other		3	3%
TOTAL			**110**	**100%**

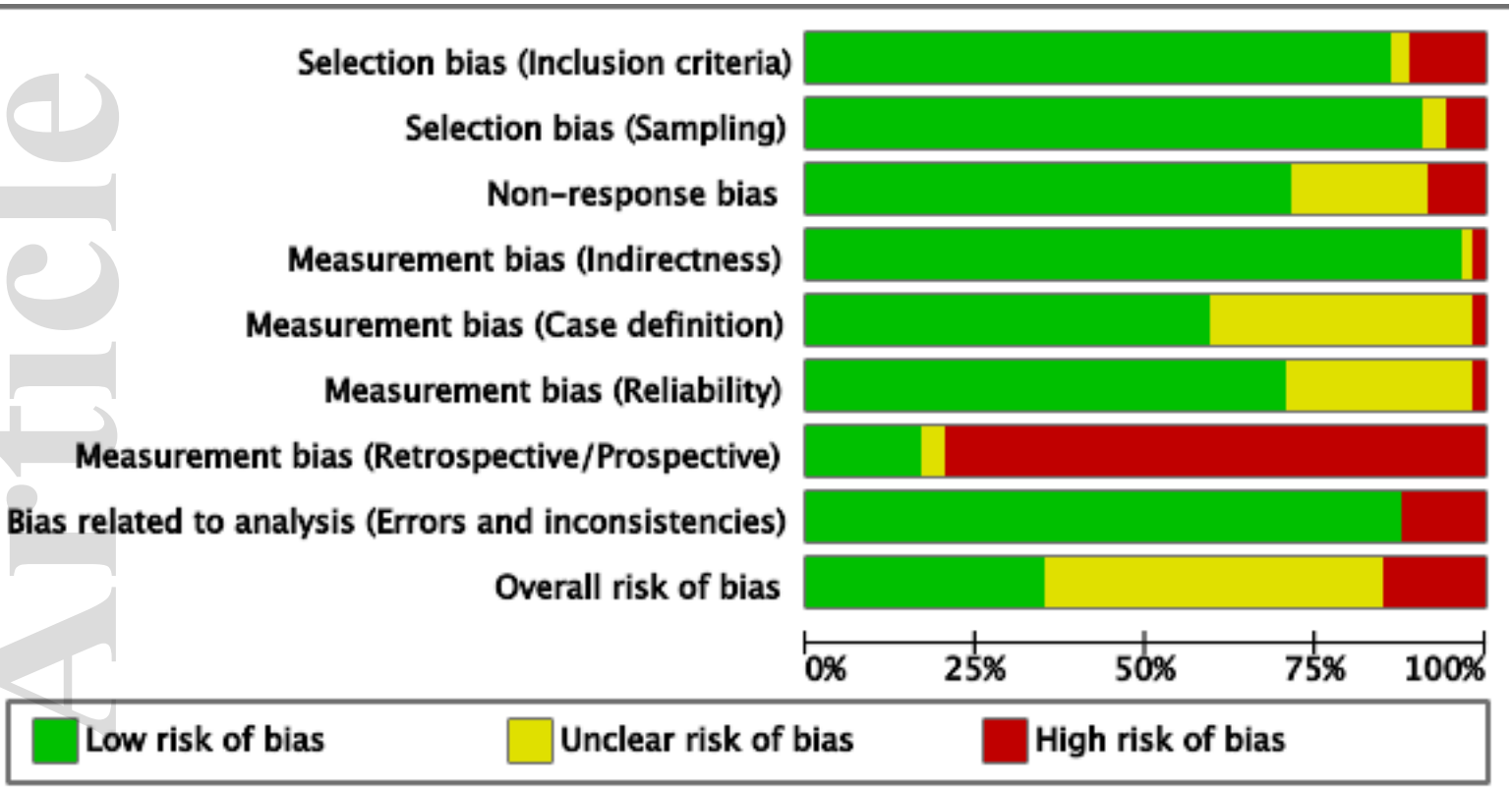
Table 1: Characteristics of included studies. Cohort and case-series 'other' includes studies with mixture of prospective and retrospective data collection and those where the text is unclear as to whether the data collection was retrospective or prospective. 'Other' specialty includes studies that reported multiple specialties in the same study. 'Other' publication type includes conference podium and poster presentations.

SPECIALITY	PROPORTION OF HEAD AND NECK EXCISIONS % (95% CI)	PROPORTION OF LESIONS RECONSTRUCTED WITH % (95% CI)		
		Direct closure	Skin graft	Flap
DERMATOLOGY	84·7 (74·7-92·6)	89·3 (85·5-92·6)	2·9 (1·8-4·4)	6·1 (4·7-7·7)
PLASTIC SURGERY	92·7 (86·2-97·3)	55·5 (42·8-66·8)	16·4 (9·9-24·2)	22·6 (11·6-36·0)
GENERAL PRACTICE	31·0 (20·0-43·1)		Not reported	
MAXILLOFACIAL SURGERY	97·7 (85·2-100)	48·6 (44·2-53·0)	24·6 (21·0-28·6)	26·8 (23·1-30·8)
EAR, NOSE AND THROAT SURGERY	100 (96·6, 100)		Not reported	
OPHTHALMOLOGY	100 (98·8-100)	72·2 (64·9-78·5)	13·0 (8·6-19·0)	11·1 (7·1-16·9)

Table 2: The proportion of lesions excised from the head and neck, and the way all lesions were reconstructed from the included studies. How lesions which were excised by general practitioners and ear, nose and throat surgeons were reconstructed was not reported in any studies.

PRISMA 2009 Flow Diagram





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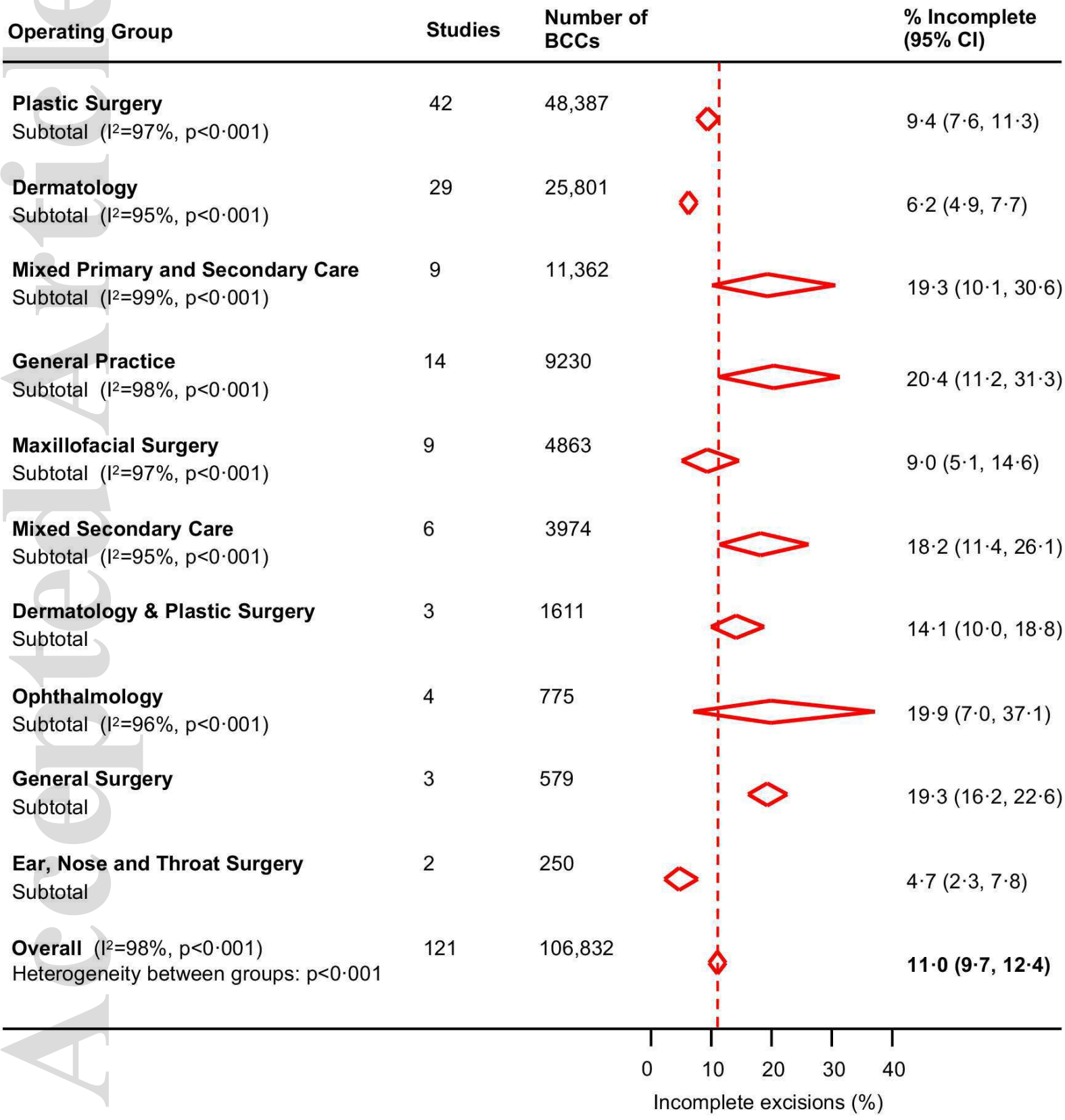
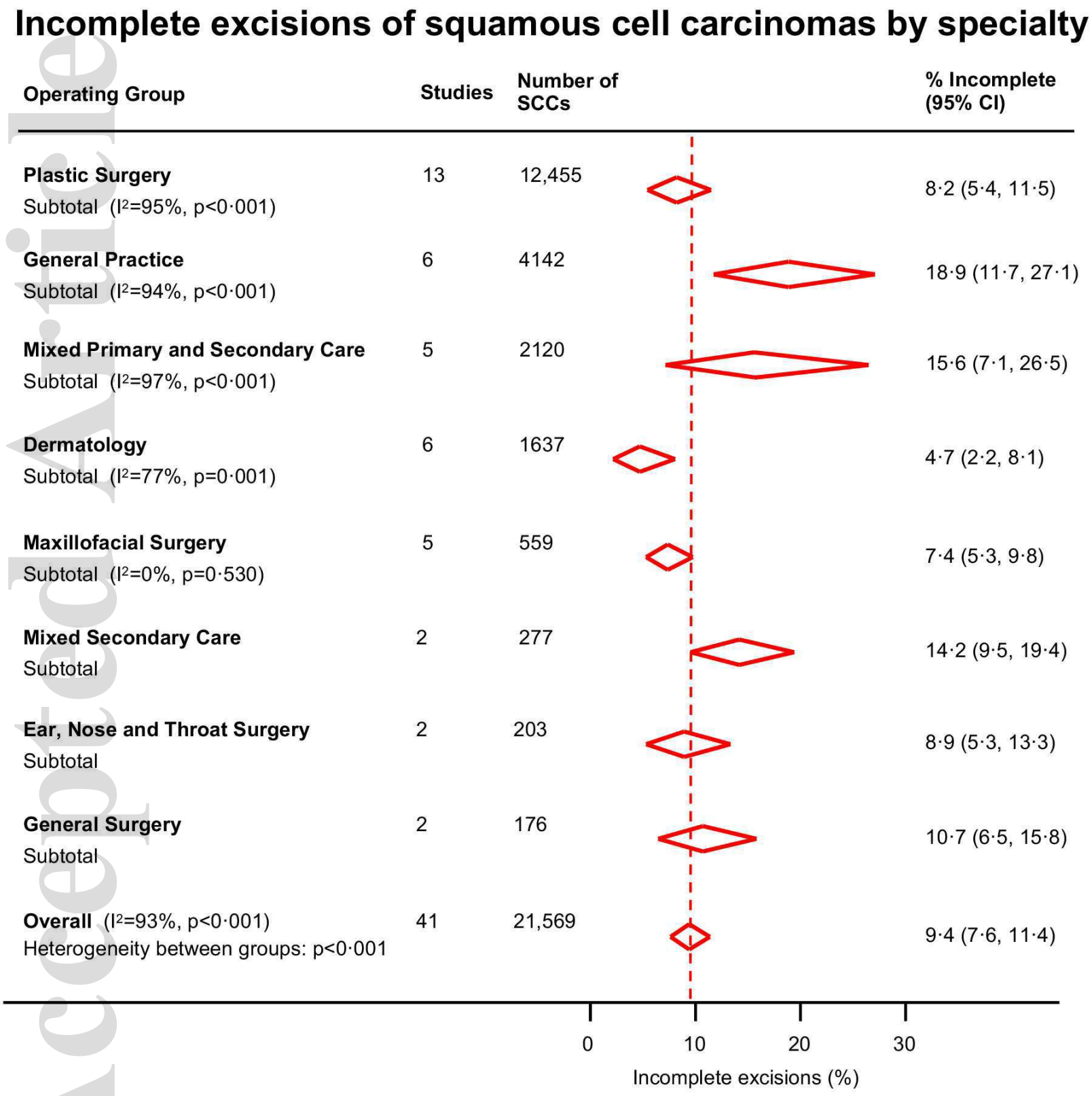
Incomplete excisions of basal cell carcinomas by specialty





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