AN EVIDENCE BASED APPROACH TOWARDS OPTIMISING THE MANAGEMENT OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE SKIN

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DEDICATION

This thesis is dedicated to the memory of my beloved father, who would love to have been with me on this journey.

ABSTRACT

Cutaneous squamous cell carcinoma (SCC) is a common cancer yet its treatment is under-researched. The objective of this thesis was to develop a proposal for a randomised controlled trial (RCT) to address uncertainties relating to the management of the condition, and to ultimately improve the management of affected patients.

Two systematic reviews were initially conducted to appraise the current evidence base for SCC treatments. Only one RCT was eligible for inclusion in the Cochrane systematic review; a small study which found no significant difference in time to recurrence between patients treated with post-operative 13-cis retinoic acid and interferon, and those not receiving adjuvant treatment. Systematic review and meta-analysis of observational studies included 118 studies. Pooled estimates of recurrence were lowest after cryotherapy and curettage and electrodesiccation, although lesions treated by these modalities were mostly small and low-risk. Although pooled recurrence after Mohs surgery appeared lower than after conventional excision or radiotherapy, the differences were not significant with overlapping 95% confidence intervals. For photodynamic therapy, pooled recurrence after apparently successful initial treatment was particularly high (26%). Evidence relating to the effectiveness of topical and systemic treatments was very limited. Estimates of recurrence were used to inform the sample size calculation for the proposed RCT.

A survey of healthcare professionals was conducted to establish research priorities and identify clinically important management uncertainties from which initial trial scenarios were formulated. High-risk SCCs were identified as a research priority, with optimal surgical management and the role of adjuvant radiotherapy being key areas of uncertainty. Through multi-disciplinary collaboration, a proposal for a two-stage RCT has been developed; in the first stage, locoregional recurrence after conventional surgery with a controlled excision margin will be compared with Mohs surgery, and in the

second stage locoregional recurrence will be compared between patients treated with adjuvant radiotherapy versus those receiving no adjuvant treatment.

Feasibility work conducted during the development of the trial has involved:

a) A retrospective analysis of SCCs treated over twelve-months to determine the number of patients and types of SCCs potentially eligible for recruitment into the proposed trial and to further inform the sample size calculation. Within five years of treatment 6% of 357 patients experienced local recurrence, 3% had regional recurrence and 1.5% died of their SCC. Comparison of the most recent American Joint Cancer Council (AJCC7) and an alternative Brigham and Women's Hospital (BWH) classification showed that approximately 50% of SCCs were T2 in both schemes and eligible for entry into the first stage of the proposed trial. However, an additional BHW T2b substage better stratified outcomes dependent on the number of risk features, and indicated that 19% of all SCCs would potentially be also eligible for the second stage of the trial.
b) A questionnaire and focus group study to assess the acceptability of the RCT and to identify possible barriers to recruitment. Participants had a desire to be better informed about SCC, wanting information relating to the trial to be provided in a variety of formats. 71% of participants were hypothetically willing to be randomised into the surgical stage of the proposed trial but had more concerns about the second stage involving adjuvant radiotherapy. Lack of equipoise and confusion about the concept of randomisation will need to be carefully addressed when presenting the trial to participants.

The proposed trial will be the first to directly compare treatments for the types of SCC seen commonly in clinical practice. For the trial to be adequately powered, an estimated 5400 participants will need to be recruited, so a multi-centre, multi-disciplinary approach will be necessary.

PUBLICATIONS AND PRESENTATIONS

Publications arising directly from this research:

Lansbury L, Leonardi-Bee J, Perkins W, Goodacre T, Tweed JA, Bath-Hextall FJ. Interventions for non-metastatic squamous cell carcinoma of the skin. **Cochrane Database Syst Rev**. 2010 (4):CD007869.

Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. **BMJ** 2013;347:f6153.

Other publications connected with this thesis:

The Evidence Update Advisory Group. Improving outcomes for people with skin tumours including melanoma: Evidence update (October 2011). National Institute for Health and Clinical Excellence. Available from www.evidence.nhs.uk

Lansbury L, Bath-Hextall F. What's new in skin cancer? An evidence-based update. **Dermatological Nursing** 2012; 11 (1): 36-38

Williams HC, Bigby M, Herxheimer A, Naldi L, Rzany B, Dellavalle R, Ran Y, Furue M (editors) Evidence-Based Dermatology (third edition), 2014, John Wiley & Sons Ltd (Chapter 32: Treatment of squamous cell carcinoma by **L Lansbury**, W Perkins, F Bath-Hextall)(In press)

Conference abstracts arising from this thesis:

7-10 April 2010: **13th World Congress on Cancers of the Skin,** Madrid. Interventions for non-metastatic squamous cell carcinoma of the skin – a Cochrane systematic review (poster)

24-26 October 2011: **Evidence 2011**, London. A systematic review of observational studies of treatments for primary non-metastatic squamous cell carcinoma of the skin – challenges to improve the evidence (poster)

8 March 2012: **East Midlands Cancer Network Skin Network Site Specific Group Educational meeting.** A twelve month audit of squamous cell carcinomas in Nottingham (oral presentation)

15-16 April 2013: **2nd European JBI Regional Symposium**, Coimbra, Portugal**.** Interventions for non-metastatic squamous cell carcinoma of the skin: a systematic review and pooled analysis of observational studies (oral presentation)

21-23 October 2013: **2013 JBI International Convention**, Adelaide, Australia. Interventions for non-metastatic squamous cell carcinoma of the skin: a systematic review and pooled analysis of observational studies (oral presentation)

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
AK	Actinic keratosis
ART	Adjuvant radiotherapy
BAD	British Association of Dermatologists
BAPRAS	British Association of Plastic Reconstructive and Aesthetic Surgeons
BSDS	British Society of Dermatological Surgeons
BWH	Brigham and Women's Hospital
BCC	Basal cell carcinoma
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
CEBD	Centre of Evidence Based Dermatology
CED	Curettage and Electrodesiccation
CONSORT	Consolidated Standards of Reporting Trials
CSG	Clinical Studies Group
EBM	Evidence based medicine
ENCR	European Network of Cancer Registries
5-FU	5-fluorouracil
HCP	Healthcare Professional
HPV	Human papilloma virus
IARC	International Agency for Research on Cancer

IFN	Interferon
LSMDT	Local skin cancer multidisciplinary team
MMS	Mohs micrographic surgery
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMSC	Nonmelanoma skin cancer
NRES	National Research Ethics Service
PDT	Photodynamic therapy
PNI	Perineural invasion
PPA	Prospective preference assessment
QoL	Quality of life
RDEB	Recessive dystrophic epidermolysis bullosa
RCPath	Royal College of Pathologists
RCR	Royal College of Radiologists
RCT	Randomised controlled trial
REC	Research ethics committee
SCC	Squamous cell carcinoma
SOeN	Site oriented e-network
SSMDT	Specialist skin cancer MDT

STROBE	Strengthening the reporting of observational studies
TNM	Tumour Node Metastasis
UICC	Union for International Cancer Control
UKACR	United Kingdom Association of Cancer Registries
UKDCTN	UK Dermatology Clinical Trials Network

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CHAPTER 1:

CUTANEOUS SQUAMOUS CELL CARCINOMA

BACKGROUND

1 BACKGROUND

1.1 Definition

Squamous cell carcinoma of the skin (SCC) is a type of non-melanoma skin cancer (NMSC) which arises from keratinocytes in the epidermis of the skin (Figure 1). The presence of malignant cells in the dermis that have breached the epidermal basement membrane is characteristic of SCC, thus making the distinction between invasive SCC and the precursors of SCC an architectural one rather than histological.

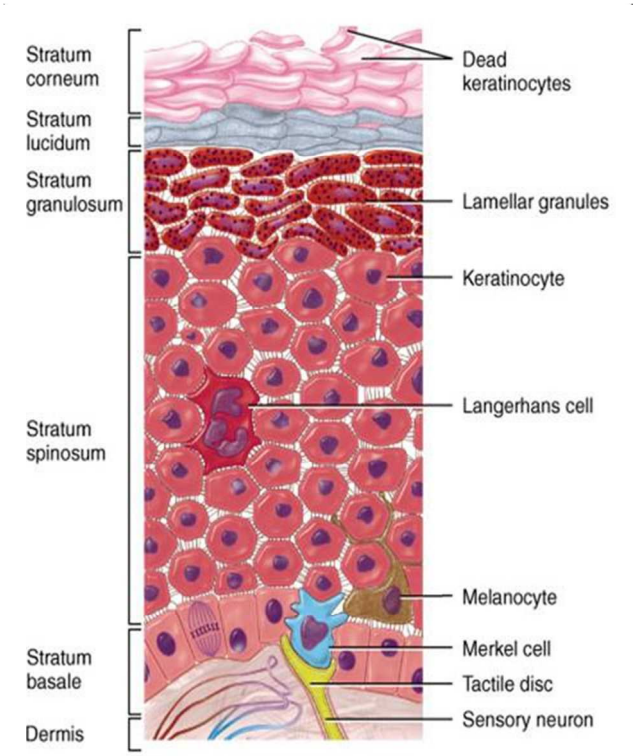


Figure 1: Diagrammatic representation of the architecture of the epidermis of normal skin

Invasive SCC has the potential to cause significant local tissue destruction, may metastasise to regional lymph nodes and distant organs, and occasionally may cause death.

1.2 Epidemiology

1.2.1. Incomplete registration

Cutaneous SCC is the second most common cancer in the world, with only basal cell carcinoma (BCC), the most prevalent kind of nonmelanoma skin cancer, being more common. Lack of standardisation of data collection and incomplete registration of non-melanoma skin cancer confound accurate comparisons of incidence in different regions. Recommendations from the European Network of Cancer Registries (ENCR)(European Network of Cancer Registries, 2000), The United Kingdom Association of Cancer Registries (UKACR)(United Kingdom Association of Cancer Registries, 2013), and the International Agency for Research on Cancer (IARC)(International Agency for Research on Cancer, 2004) are that only the first NMSC of each histological type is registered per individual. However, cancer registries vary in their completeness of SCC registration. In Scotland, the aim is to register all SCCs, not just the first diagnosed, and similarly in Ireland although in practice only the first ones are recorded there (National Cancer Intelligence Network, 2013). However, in Wales lack of resources precludes registration of even first SCCs so the UKACR standard is not met (National Cancer Intelligence Network, 2013).

By registering all malignant skin cancers over a one year period in the South West of England onto a pilot standalone skin cancer dataset and comparing the number of cancers with those registered on the South West Public Health Observatory Cancer Registry (the lead cancer registry for skin in England and Wales), it has been estimated that almost 30% of SCCs go unrecorded (Poirier et al.). This is likely to be a reflection of second and subsequent SCCs for which there is currently no requirement to be registered, and concurs with other studies that have attempted to compare number of SCCs treated with those actually recorded on cancer registries (van der Geer et al., 2013).

Apart from subsequent SCCs, a number of new SCCs are slipping through the registration net. Significant variation between registries in recording NMSCs

has been shown, ranging from 12% to up to 44% of SCCs failing to be recorded (Lucke et al., 1997, Brewster et al., 1996), although these studies are now quite old. More recently, the South West Public Health Observatory Network estimated a range of expected number of NMSCs for Cancer Networks across England by multiplying the incidence of malignant melanoma in each area by seven and 10, demonstrating that under-completeness of new NMSC recording is particularly marked in London and the south-east of England compared with other English cancer registries (South West Public Health Observatory, 2010). A survey conducted on behalf of the National Cancer Intelligence Networks found that a costly and labour-intensive registration process, lack of efficient electronic systems and low use of the Royal College of Pathologists' histology reporting proforma were barriers to registering SCC and other types of NMSC (National Cancer Intelligence Network, 2010). Furthermore, some SCCs may escape registration if they are treated privately, or if they are not recognised as SCCs and are treated without pathological confirmation, although the vast majority of SCCs are believed to confirmed histologically (Lucke et al., 1997).

1.2.2. International variation

Worldwide the highest incidence of SCC is found in Australia where population based epidemiological surveys suggest age standardised incidence rates of more than 1000 cases per 100 000 per population per year (Green et al., 1996, Buettner and Raasch, 1998, Staples et al., 2006). In the United States incidence rates range from 32 and 155 per 100 000 population for males, and 8 to 29 per 100 000 population for females (Miller and Weinstock, 1994, Diepgen and Mahler, 2002), which although far less than those seen in Australia is generally higher than age-standardised rates seen across northern Europe where recorded incidence rates range from 11 to 46 per 100 000 per population for males and from 5 to 23 per 100 000 for females (Hoey et al., 2007, Brewster et al., 2007b, Holme et al., 2000, Katalinic et al., 2003, Hussain et al., 2010). Variations in incidence are also seen within countries and almost certainly reflect differences in ultraviolet radiation exposure at different

altitudes or the distribution of susceptible ethnic groups within the country (Lomas et al., 2012).

Several studies have reported rising incidence rates in various parts of the world of between 2 and 11% per year in the latter part of the twentieth century (Glass and Hoover, 1989, Gloster and Brodland, 1996, Demers et al., 2005, Karagas et al., 1999, Holterhues et al., 2010, Staples et al., 2006). Between 1985 and 1992, the incidence of SCC more than doubled across Australia as a whole (Staples et al., 2006), and in the United States the incidence increased threefold (Miller and Weinstock, 1994). Similarly a systematic review of the worldwide incidence of NMSC has shown a trend towards increasing incidence rates of SCC across Europe, albeit not such rapid increases as the rates seen for BCC (Lomas et al., 2012). The National Cancer Intelligence Network has shown that across the UK as a whole, there was an increase in the incidence of SCCs from 2000-2002 to 2008 to 2010 of 34% in males and 39% in females (National Cancer Intelligence Network, 2013), some of which may be attributable to more complete registration although this is unlikely to account for all the increase.

Some studies suggest that incidence rates of SCC may be stabilising in subgroups of the population. A Canadian study found that there was a trend towards stabilisation of invasive SCC rates in 1995 (annual percentage change 0.36%)(Jung et al., 2010), a finding which is consistent with a study of incidence in south-eastern Arizona where SCC incidence plateaued or even declined slightly between 1985 and 1996 (Harris et al., 2001). There was also no significant difference between world age-standardised incidence rates for SCCs between 1988 and 1998 in West Glamorgan in South Wales, although BCC incidence had increased significantly over the same period (Holme et al., 2000). In Northern Ireland age-adjusted incidence in females remained steady at 22 per 100 000 population between 1993 and 2002, although rates in men increased from 41 to 48 per 100000 population over this time (Hoey et al., 2007), and in New Zealand where the overall annual incidence of SCC had increased by 1.1% between 1997 and 2007, the only subgroup in which there

was a significantly increased annual percentage was men over 80 years (Brougham et al., 2011). Of particular interest is the finding that in Australia, although there has been an overall increase in the incidence of NMSC since 1985, there appears to have been no significant increase in the incidence of SCC in people under 50 years of age or BCC in those under 60 (Staples et al., 2006). Furthermore, although the number of NMSCs treated in Australia between 1997 and 2010 increased by 86%, and is estimated to increase by a further 22% between 2010 and 2015, there was a relative decrease in the number of treatments in people aged 45 years when taking into account the 15% increase in population growth in this age group. It is in the older age groups where the impact of increased incidence will be greatest, with the number of skin cancer treatments for those aged 65 to 74 years and ≥75 years predicted to have increased by 171% and 215% respectively by 2015, far outstripping the predicted population growth of 57% and 68% respectively in these groups (Fransen et al., 2012). As those under 50 years of age were among the first generation to receive cancer education programmes such as the 'Sunsmart' campaign, the results of these studies are providing early evidence of the value of such public health campaigns and their potential impact on future generations. In an economic evaluation of the SunSmart programme in the Australian state of Victoria, where the scheme was originally instigated in the 1980s, it has been calculated that between 1988 and 2003 more than 94000 NMSCs and 9000 melanomas were averted as a result of the campaign, with prevention of more than 1000 deaths from all types of skin cancer (Shih et al., 2009). However, the effectiveness of the programme on NMSC was only based on the change in the age-specific BCC rate, and not SCC, as an earlier study had failed to show any impact on SCC whereas a decrease in BCC had been demonstrated in people under 50 years old (Staples et al., 1998). Nonetheless, the authors of the economic evaluation argue that sustained modest investment in the skin cancer programme is excellent value for money and that with an upgraded national Australian programme for the forthcoming 20 years 120 disability-life-years will be averted with associated reductions on the use of health care resources

(Shih et al., 2009). The 'Sunsmart' campaign has a high profile in Australia; elsewhere in the world skin cancer programmes are varied and dependent on funding and input from government sources and non-government sectors. Since the mid-1990s there have been several public health awareness campaigns in the UK, the first of which was the 'Sun Know How' campaign delivered by the Health Education Authority until 2000. In 2003, Cancer Research UK was commissioned to run the SunSmart UK campaign, with different audiences, such as outdoor workers, teens and holidaymakers targeted each year. Other UK charities and professional organisations have run their own sun-awareness programmes, such as the BAD Sun Awareness Campaign (www.bad.org.uk/for-the-public/sun-awareness-campaign), Teenage Cancer Trust 'Shunburn' campaign (www.teenagecancertrust.org/what-we-do/education/shunburn/), and the Karen Clifford Skin Cancer Charity (SKCIN) 'Sun Safe Schools' and 'Sun Safe Workplaces' campaigns (www.skcin.org/Sun-Safety/How-to-Prevent-Skin-Cancer), whilst other skin charities such as the British Skin Foundation promote sun awareness messages on their website (www.britishskinfoundation.org.uk/SkinInformation/SkinCancer.aspx). It will be interesting to evaluate the impact of skin cancer awareness campaigns in other countries in the future. A survey on the overall impact of the 'SunSmart UK' campaign between 2003 to 2008 reported that there had been a significant increase in awareness of the importance of protecting children (5.2% to 12.4%), checking moles (8.3% to 11.0%), avoiding sunburn (5.4% to 11.7%), seeking shade (34.8% to 41.0%), covering up (26.8% to 39.9%) and avoiding sunbeds (1.2% to 7.5%), although no significant change in peoples' attitudes to their perceptions of the benefits or risks of the sun was seen (Cancer Research UK, 2008). However, generally the evidence for what type of skin cancer prevention activity works in the UK population is limited, although evidence from Australia suggests that long-term commitment and investment with regular reinforcement of key messages will be important if sustained changes are to made and the risk of developing skin cancer is to be reduced in the population (Dobbinson et al., 2008).

1.2.3. Incidence in the United Kingdom

The most recent figures available from Cancer Research UK indicate that in 2010, when the population of the UK was 62.3 million, there were almost 100,000 new cases of NMSC registered in the United Kingdom with just under 13,000 new cases of malignant melanoma (Cancer Research UK, 2013) (Figure 2). This would equate to approximately 25000 new cases of SCC, based on a ratio of SCC: BCC of 1:4. However, as discussed above the number of registered NMSCs is likely to be a significant underestimate.

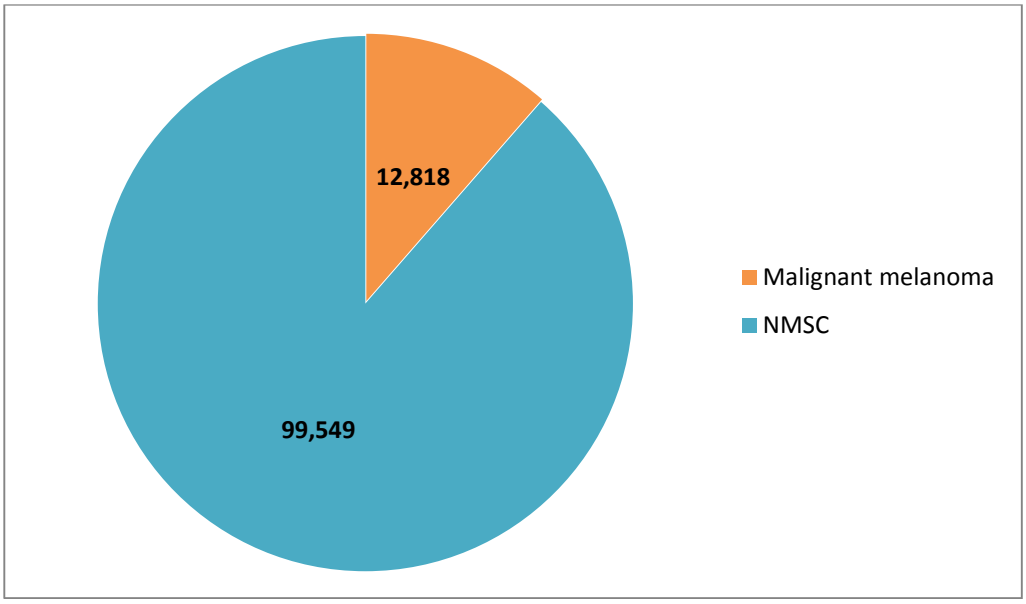


Figure 2: New cases of skin cancer during 2010

Based upon Australian figures indicating the occurrence of one melanoma for approximately every 64 NMSCs, it has been suggested that true numbers of NMSC in the UK may actually be closer to the 800,000 seen annually in Australia (Sinclair, 2013). However, this is based on the assumption that the ratio of melanoma: nonmelanoma is of a similar magnitude in Australia and the UK, which cannot be assumed as UV exposures are different and there may be inherent differences between the populations in each country, and is significantly greater than the rate-ratio of seven to 10 indicated by the majority of Local Authorities in the South-West and West Midlands and which was used by the South West Public Health Authority to estimate the number

of NMSCs across Cancer Networks in the UK (South West Public Health Observatory, 2010).

In 2010 there were 590 deaths attributed to NMSC in England and Wales (Cancer Research UK, 2013), most of which would be due to SCC, with smaller numbers resulting from BCC and other NMSCs such as Merkel Cell Carcinoma, although the data available does not categorise deaths according to type. Furthermore, a recent retrospective study of cases of fatal cases of SCC recorded over an 11-year period, has highlighted the potential inaccuracy of death certification data that is recorded as being due to SCC, with 13 of 58 (22%) reported cases being due to other causes, particularly malignant adnexal tumours, and only 21 of 58 (36%) cases being definitely attributed to SCC (Rose et al., 2013).

1.3 Clinical Features

1.3.1. Presentation

SCC frequently arises in areas of the skin where there is evidence of pre-existing photodamage such as actinic keratosis (AK), irregular pigmentation, hyperkeratosis and telangiectasia. Induration of the skin, usually not sharply defined and extending beyond visible tumour, is an early sign of SCC development. The tumour itself may appear as an enlarging firm papule, plaque, nodule or ulcer although clinical appearance and behaviour varies with site of origin (Figure 3, Figure 4, Figure 5). SCCs which arise on mobile parts of the body such as the lip may initially appear as a fissure or small ulcer which fails to heal and bleeds intermittently. Subungual SCCs, although rare, may be mistaken for other conditions, resulting in delayed diagnosis and often only correctly diagnosed once the tumour has invaded the distal phalanx sufficient to cause radiological changes.

Well-differentiated tumours may appear papillomatous with a keratotic crust, which when shed reveals an ulcerated or eroded tumour underneath that bleeds easily when traumatised.

Invasive SCCs can be asymptomatic, although the patient may experience pruritus, tenderness, pain and bleeding. Perineural involvement may be indicated by pain, paraesthesia, anaesthesia or weakness, and on rare occasions such symptoms may precede visible signs of tumour (Schroeder et al., 1998).

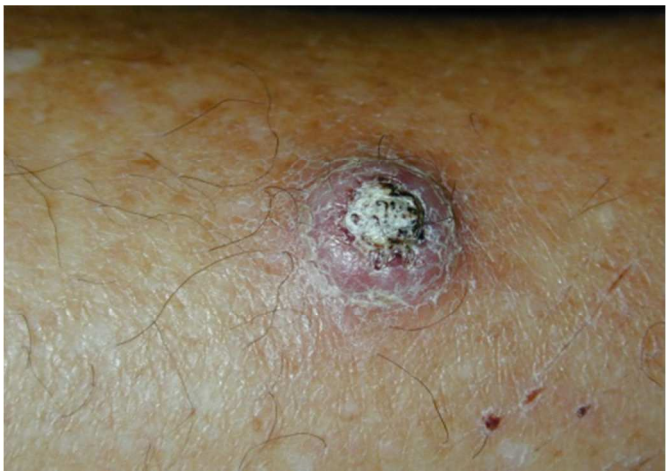


Figure 3: A well-defined SCC with central hyperkeratosis

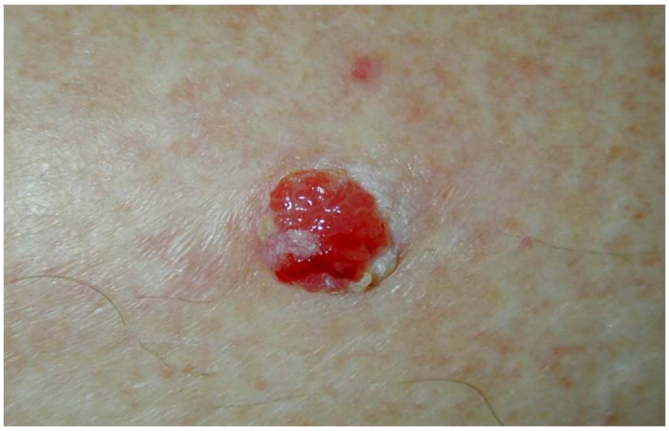


Figure 4: Raised erythematous invasive SCC on a light-exposed site in an elderly patient

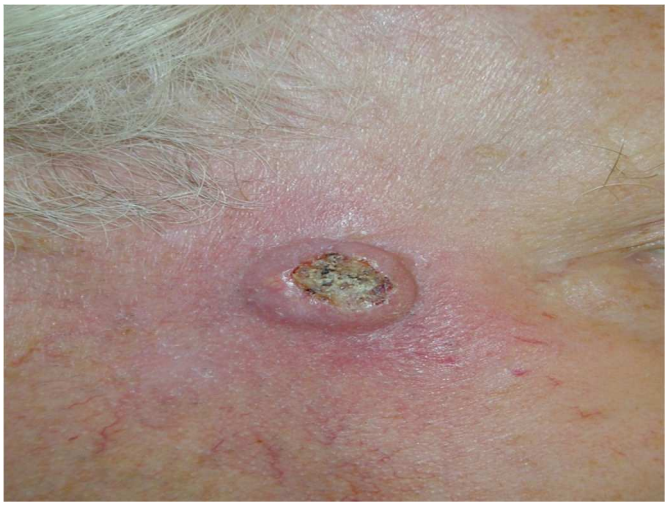


Figure 5: An elevated hyperkeratotic SCC of the temple with surrounding erythema (images reproduced with kind permission of Dr William Perkins, consultant dermatologist, Circle HHS Treatment Centre, Nottingham)

1.3.2. Variants of SCC

The term 'squamous cell carcinoma' encompasses a number of variants as part of a heterogeneous group of tumours which display much variation in terms of clinical behaviour and aggressive potential (Cassarino et al., 2006b, Cassarino et al., 2006a). Some of these rare variants warrant separate mention in view of their tendency to cause extensive local tissue destruction or by having a particular propensity to metastasise.

Epithelioma cuniculatum

Verrucous SCC is a rare variant of SCC that may be found at any cutaneous site but the plantar surface of the foot is the most usual site of presentation (epithelioma cuniculatum) (Aird et al., 1954), where it may be initially misdiagnosed as a plantar wart. Growth is slow, but it eventually develops into a large exophytic mass with multiple sinuses opening on the surface, with release of greasy foul-smelling material if squeezed. Although it causes extensive local tissue destruction, metastases from epithelioma cuniculatum are uncommon.

Squamous cell carcinoma arising in chronic conditions

SCC may arise in areas of chronically damaged skin such as long-standing ulcers or burn scars (Marjolin's ulcer) (Da Costa, 1903, Treves and Pack, 1930)(Figure 6, Figure 7), sinus tracts (Pilipshen et al., 1981) or osteomyelitis (Kirsner et al., 1996), or in chronic inflammatory conditions such as discoid lupus erythematosus (Sulica and Kao, 1988), lupus vulgaris (Motswaledi and Doman, 2007) and dystrophic epidermolysis bullosa (Weber et al., 2001, Mallipeddi, 2002).

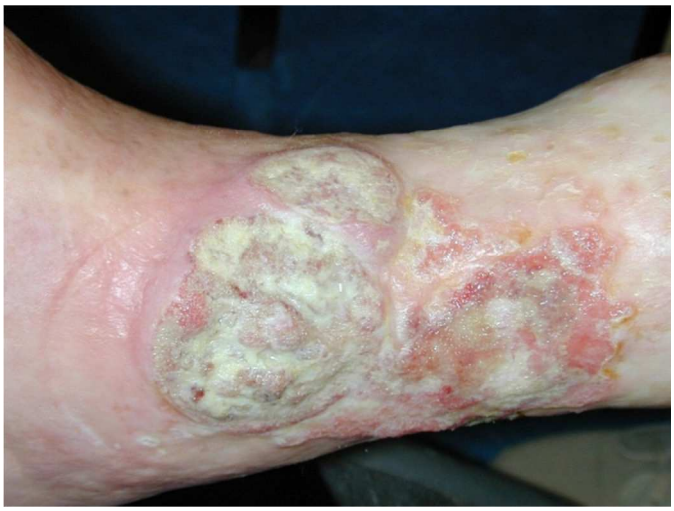


Figure 6: SCC arising in a long-standing ulcer (image courtesy of Dr W Perkins)

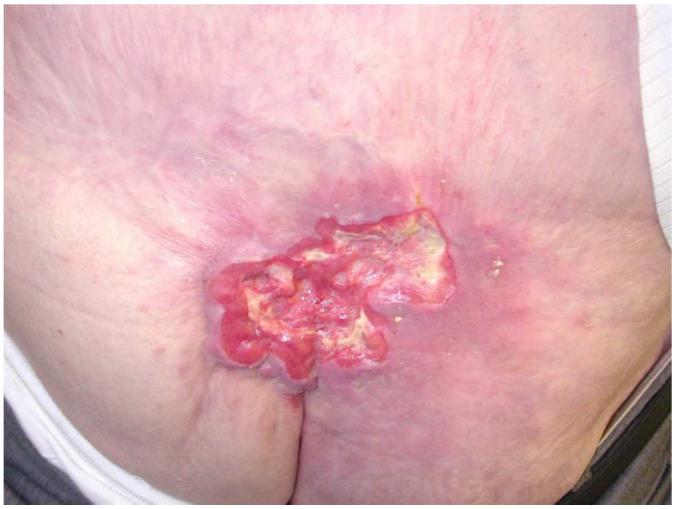


Figure 7: SCC arising in an old burn scar (image courtesy of Dr W. Perkins)

Although rare, they are typically aggressive with between 36% and 54% of SCCs arising in chronically damaged areas metastasising to regional lymph nodes despite most of them having well- or moderately-differentiated histology, with survival at 5 years being only 52% to 75% (Cassarino et al., 2006a).

Spindle cell squamous cell carcinoma and radiation-associated SCC

First described in 1935 (Martin and Stewart, 1935), it was initially thought that the rare spindle cell variant of SCC primarily arose in previously irradiated areas of skin. However, it is now recognised that most cases arise on areas of sun-exposed skin, and that indeed most SCCs arising in areas of previous irradiation are conventional SCCs.

Spindle cell SCCs arising in areas of previous radiation have been reported to be more aggressive than those that are not associated with prior radiation (Cassarino et al., 2006b), although this is somewhat contentious as reports of their course have generally not described parameters such as depth of invasion, location and tumour differentiation which affect metastatic potential. Nevertheless, all types of SCC that are radiation-associated appear to have a more aggressive course, with disease-specific death rates of between 9.5% (Martin et al., 1970) and 12% (Pack and Davis, 1965) having been reported for these cancers, along with earlier and frequent recurrences, metastasis to lymph nodes and distant organs, and eventual death (Cassarino et al., 2006a). Data is, however, lacking for subtypes of radiation-associated SCCs. Given the lack of reliable data regarding the prognosis of spindle cell SCC, British Association of Dermatologists (BAD) guidelines (Motley et al., 2002)and the World Health Organisation (WHO) (Le Boit et al., 2006) regard all spindle cell variants as high-risk, in addition to other types of SCCs in areas of prior irradiation, whereas the American AFIP considers spindle cell SCCs to be high-risk only if associated with radiation exposure (Patterson and Wick, 2006). Taking these uncertainties into account, the Royal College of Pathologists' (RCPath) most recent dataset for reporting primary cutaneous SCC includes all spindle cell SCC variants as being potentially high-risk (Chaudhuri et al., 2006).

Desmoplastic squamous cell carcinoma

By definition, desmoplastic SCC variants have a dense stromal response with growth of fibrous tissue around the tumour occupying at least 30% of the tumour volume. They are rare and again data is sparse regarding their prognosis, but of the studies that have investigated this, the conclusion appears to be that they tend to be more aggressive than conventional SCCs. A prospective study of 594 SCCs of which 44 were desmoplastic reported recurrence and metastasis of 27% and 23% respectively for desmoplastic SCCs compared with 4% and 3% for other types of SCC (Breuninger et al., 1997). Other studies have reported metastases in up to 77% of desmoplastic SCCs.

Desmoplasia has also been shown to be an independent predictor of local recurrence (Brantsch et al., 2008). These SCC variants are thus considered to be high-risk in the BAD guidelines (Motley et al., 2002) and by the RCPath (Chaudhuri et al., 2006).

Acantholytic squamous cell carcinoma

Also known as adenoid or pseudoglandular SCC, between 2% and 4% of all cutaneous SCCs are acantholytic variants characterised histologically by the loss of intercellular bridges. The metastatic potential of acantholytic SCC may be higher than SCCs of no special type, but data is sparse. However, there have been reports of mortality from this SCC variant in between 3 % to 19% of patients (Johnson and Helwig, 1966, Nappi et al., 1989), so for the purposes of assigning degree of risk the BAD Guidelines, WHO and RCPath consider SCCs classified as acantholytic to be high-risk (Motley et al., 2002, Le Boit et al., 2006, Chaudhuri et al., 2006)

1.3.3. Differential diagnosis

Diagnosis of a well-differentiated SCC arising in area of photodamaged skin is usually straightforward, but needs to be distinguished from a keratoacanthoma which is generally considered to be a distinct entity from invasive SCC, which tends to grow very rapidly with a domed appearance and regresses spontaneously within 6 months. Other lesions included in the differential diagnosis include BCC, amelanotic malignant melanoma, actinic keratosis, inflammatory ulcers, granulomas and viral warts and verrucae.

1.4 Natural history and progression

In white-skinned individuals, SCCs most commonly present on sun-exposed areas, with 50 % to 70% occurring on the head and neck (Marks, 1996, Sober, 1983). There is a strong association between the presence of precursors of SCC, actinic keratosis and SCC *in situ* (Bowen's disease), which are indicators of sun-damaged skin, and the development of SCCs. Histological analyses of invasive SCCs suggest that between 26% and 72% arise from AK (Mittelbronn et al., 1998, Marks et al., 1988, Czarnecki et al., 2002). It is debateable how

frequently AKs transform into SCC and appears to depend upon the extent of sun-damage and to be time dependent. Although 10% to 15% of individual AK lesions regress spontaneously (Marks et al., 1986, Harvey et al., 1996), a review of studies published between 1988 and 1998 found that the overall risk of AKs transforming ranged from 0.025% up to 16% per year (Glogau, 2000). In a more patient-centred approach, one study has suggested that for a patient with approximately 8 AKs, the probability of at least one of them transforming during a 10 year period is 10% (Dodson et al., 1991). A retrospective analysis of pathologically confirmed AKs which progressed to invasive SCC at the same site indicated that, for those AKs which do progress, it takes approximately 2 years for progression to occur (95% confidence interval 21.04 to 28.16 months) (Fuchs and Marmur, 2007). This study was limited however by the small number of SCCs which were judged to have arisen from an AK (n=91), and was not able to account for time lags in the diagnosis of AKs and SCCs, and may have excluded patients in whom AKs were present at the site of an SCC but which had not been biopsied and pathologically proven. Clinically, it is not yet possible to determine which AK lesions are likely to develop into SCCs, so some professional bodies such as the American Academy of Dermatology advocate treating all AKs (1999). However, the most recent AK management guidelines from the British Association of Dermatologists (BAD) recommend that the decision whether to treat or not should be made on an individual basis according to signs, symptoms and history as there is currently insufficient evidence to justify treating all AKs, and that thin AKs may warrant no treatment (de Berker et al., 2007). SCC *in situ* (Bowen's disease), in which dysplastic cells fill the entire thickness of the epidermis, also has the potential to progress to SCC, with an estimated 3% to 5% of lesions progressing to invasive SCC (Peterka et al., 1961, Kao, 1986). These data are again drawn from retrospective studies, and may not be an accurate reflection of true progression rates as many patients with Bowen's disease may not seek medical advice or may be treated in primary care without pathological confirmation. There are several treatment options for SCC *in situ* from topical creams to surgery and PDT, although some

thin, slowly progressing lesions, particularly those on the lower leg, may warrant observation rather than aggressive intervention (Morton et al., 2014).

Squamous cell carcinomas generally grow at a faster rate than BCCs, although not as rapidly as keratoacanthomas which resolve spontaneously if left untreated.

Invasive SCC (Rowe et al., 1992) has the potential to recur and to metastasise, with an overall 5-year recurrence rate of 8% for primary cutaneous lesions, and a 5-year rate of metastasis of approximately 5%. Metastases from cutaneous SCC are most frequently seen in the regional lymph nodes initially, followed by the lungs, liver, and other organs. Factors favouring metastasis include tumour site, depth, diameter, rate of growth, histological differentiation, perineural, lymphatic and vascular invasion, and host immunosuppression (Motley et al., 2002). Later chapters in this thesis include a detailed discussion of outcomes and prognostic features of cutaneous SCC so will not be described further in this section.

1.5 Risk factors

The risk of developing SCC depends on the inter-relationship between extrinsic factors and the individual's response to these. Intrinsic and extrinsic risk factors are summarised in Table 1.

Table 1: Risk factors for development of SCC

Host-related Factors	Extrinsic Factors

• Older age	• Ultraviolet radiation:
	  ○ Cumulative sunlight exposure
	  ○ Sunbed use
	  ○ Medical UV treatment

• Male gender	

• Fair complexion:
  ○ Red/blond hair
  ○ Hazel/blue eyes
  ○ Fitzpatrick skin types I and II	

• Genetic conditions:
  ○ Albinism
  ○ Xeroderma pigmentosum
  ○ Recessive epidermolysis bullosa
  ○ Epidermodysplasia verruciformis
	• Chemical carcinogen exposure:
	  ○ Smoking
	  ○ Arsenic
	  ○ Petroleum by-products
	  ○ Insecticides/herbicides/fungicides

• Pre-malignant skin conditions	

• History of skin cancer	• Radiation exposure:
	  ○ Ionising radiation
	  ○ Thermal radiation

• Chronic conditions:
  ○ Chronic ulcers
  ○ Burn scars
  ○ Osteomyelitis sinuses
  ○ Hidradenitis suppuritiva	

• Weakened immune system:
  ○ Organ transplant recipient
  ○ HIV/AIDS
  ○ Chronic lymphocytic leukaemia
	• Human Papillomavirus infection

1.5.1. Intrinsic (host-related) factors

Cutaneous SCC is more prevalent in older people, males and those with pre-malignant skin conditions or a prior history of skin cancer, all of which may be surrogate markers for cumulative ultraviolet radiation exposure. Phenotypic features such as red hair, lack of ability to tan and propensity to freckling are well recognised features which correlate with an individual's risk of developing SCC (Gallagher et al., 1995).

Conditions in the host that increase susceptibility

Host responses that influence the development of SCC include chronic inflammation, such as chronic ulcers and burn scars. Some individuals also have increased genetic susceptibility to SCC in certain syndromes such as xeroderma pigmentosum (Robbins, 1988) (in which the DNA repair mechanism is defective causing severe sensitivity to UV radiation and the early development of multiple SCC), albinism, and epidermodysplasia verruciformis (a rare, autosomal recessive inherited skin disorder characterised by eruptions of wart-like lesions caused by infection with the human papillomavirus) (Diepgen and Mahler, 2002). People with the inherited condition recessive dystrophic epidermolysis bullosa (RDEB), in which there is a defect in the type VII collagen gene whereby either no collagen VII or very low levels are produced resulting in a mechanically fragile skin, have a 50 times greater than normal risk of developing SCC. Approximately 90% of those with RDEB-Hallopeau-Siemens, the most generalised subtype of RDEB, will have developed cutaneous SCC by the age of 55 years (Fine et al., 2009). It is not yet known why these individuals are at increased risk, apart from them having chronic non-healing scars.

Organ Transplant Recipients and immune system compromise

Impaired host immunity is an important risk factor in the development of SCC, and as the number of successfully transplanted and longer-living organ recipients rises, SCC is a particular concern in this group. In transplant recipients, skin cancers account for 90% of all diagnosed malignancies, with SCCs being the most common type. Reversal of the SCC: BCC ratio seen in the

general population is also a feature of the skin cancers seen in this group (Hardie et al., 1980, Ramsay et al., 2002, Moloney et al., 2006).

The risk of developing SCC of the skin post-transplantation is 65 to 253 times greater than in the non-transplanted population and related to the degree of immune suppression (Hartevelt et al., 1990, Jensen et al., 1999). A more recent large cohort study from the UK in which more than one thousand ethnically diverse organ transplant recipients were prospectively followed over a 2 year period (Harwood et al., 2013), has shown a 153-fold excess risk for developing SCC and dying from it compared with the general population.

The incidence rates of SCC development increase according to the time post-transplant, with incidence rates in an Australian study rising from 23% at 5 years to 44% after 9 years (Hardie et al., 1980), and up to 70% after 20 years (Bouwes Bavinck et al., 1996); higher than the incidence rates of 10% to 15% seen at 10 years and 40% at 20 years after transplantation in European countries (Hartevelt et al., 1990, London et al., 1995, Naldi et al., 2000). Furthermore, SCCs that develop in organ transplant recipients may be more aggressive than in the general population. In a study of heart and heart plus lung recipients, 4% developed an aggressive SCC within 10 years of their transplant, with two-thirds of these developing distant metastases or dying as a result of the SCC (Veness et al., 1999).

Non-iatrogenic induced immune suppressed individuals are also at greater risk of developing SCC. This may be the result of congenital disorders, viral infection, chronic lymphocytic leukaemia, or human immunodeficiency virus (HIV). People infected with HIV have been found to be at three to five times greater risk of developing SCC than non-infected people and to develop it at a significantly younger age, but unlike organ transplant recipients there is no reversal of the BCC: SCC ratio in this group (Wilkins et al., 2006, Demopoulos et al., 2003). However, SCCs that develop in the HIV infected people do seem to have a more aggressive course, with higher risk of local recurrence, metastasis and 50% mortality (Nguyen et al., 2002).

1.5.2. Extrinsic factors

Ultraviolet radiation

Ultraviolet (UV) radiation forms part of the solar electromagnetic spectrum, and can be broadly divided into three wavelength bands: UVA (315-400nm) which is not absorbed by the earth's ozone layer; UVB (280-315nm) which is mostly absorbed by the ozone layer; UVC (100-280nm) which is completely absorbed by the ozone layer and the earth's atmosphere.

For the general population, exposure to ultraviolet (UV) radiation, usually as a result of a lifetime's sun exposure but also arising from sunbed use or as a part of medical treatment, is the most important risk factor for SCC development, with approximately 50% to 60% of SCCs resulting from UV radiation exposure (Lucas et al., 2008). Cumulative lifetime sun-exposure is strongly associated with the risk of developing SCC, in contrast to BCC where it is believed intermittent and childhood exposure are more important (Madan et al., 2010).

There is now a body of evidence suggesting a causal link between the use of sunbeds (which predominantly emit UVA) and the development of SCC. The International Agency for Research on Cancer (IARC) stated in 2011 that there was limited evidence that sunbed use was linked to the development of SCC (Cogliano et al., 2011). However, a recent meta-analysis including 12 studies with 9328 patients with NMSC in which people who had ever used an artificial indoor tanning device were compared with those who had never used one, found a positive association with SCC risk (Relative Risk (RR) 1.67 [95% CI 1.29 to 2.17])(Wehner et al., 2012).

The protective effect of skin pigmentation is reflected in the low incidence of non-melanoma skin cancer (NMSC) seen in black populations. Asian and Hispanic groups, in which skin pigmentation is intermediate, share epidemiologic and clinical features of dark-skinned and white groups, so although the incidence is higher than in black people, it does not approach that seen in white populations (Gloster and Neal, 2006, Leong et al., 1987,

Pennello et al., 2000). A national survey conducted in the United States showed an annual age-adjusted incidence for all NMSCs of 3.4 per 100,000 population for African Americans compared to 232.6 per 100,000 among whites, indicating that whites are around 70 times more likely to develop skin cancer (Scotto et al., 1981). However, the mortality among black people has been shown to be disproportionately high in comparison with incidence (Weinstock, 1993). Whereas the sun-exposed skin of the head and neck is the most common site for the occurrence of SCC in white populations, non-sun-exposed sites are more frequently involved in black people, suggesting that sunlight exposure is a less important aetiological factor in this group. The presence of chronic scarring processes and areas of chronic inflammation are the most important risk factors in blacks (Halder and Bridgeman-Shah, 1994, Mora and Perniciaro, 1981) and SCCs associated with these predisposing factors tend to be more aggressive, with a 20% to 40% risk of metastasis compared with a rate of 1% to 2% in sun-induced SCC (Mora and Perniciaro, 1981, Rowe et al., 1992).

Chemical carcinogens

Exposure to chemical carcinogens has also been shown to increase the risk of developing SCC. A recent systematic review including pooled data from 6 studies showed a significant association with smoking, with a 52% increase in odds of developing cutaneous SCC (OR 1.52, 95% CI 1.15-2.01), most pronounced in current smokers and those who had ever smoked (Leonardi-Bee et al., 2012). Prolonged exposure to arsenic is also positively associated with the development of squamous cell carcinomas, particularly of the skin and lung and is believed to result from genetic and epigenetic changes resulting in a dramatic increase in the expression of keratins (Martinez et al., 2011). Nowadays most significant exposure is via drinking water sources in various parts of the world with high natural arsenic levels rather than medicinal exposure, although this can still occur in parts of the world where arsenic may still be used in preparations such as Asiatic pills and in some Chinese herbal medicines and traditional Indian medicines (Prasad et al.,

2006). Other carcinogens which have been implicated in the development of SCC of the skin include ionising radiation, psoralen-UVA therapy, and petroleum by-products, with weaker potential associations also being made with exposure to insecticides, herbicides, fungicides and seed treatments (Lichter et al., 2000, Lindelof et al., 1999, Karagas et al., 2007, Gallagher et al., 1996).

Human Papillomavirus

Human papillomaviruses (HPV) have long been recognised as important aetiological agents in the development of cervical cancer and some types of ano-genital cancer and head and neck SCCs, but their role in the development of cutaneous SCCs has been rather more contentious. The potential role of HPV was first recognised when β-HPV was associated with the development of SCCs in the rare genetic disorder epidermodysplasia verruciformis (Majewski and Jablonska, 1995). However, whilst many studies have shown that 16% to 54% of SCCs from immunocompetent individuals are infected with HPV, the presence of HPV DNA in SCCs is not universal (Arron et al., 2011). This may in part be due to variation in the sensitivity of detection methods between studies. Other possible explanations for the lack of HPV in SCCs include the possibility that HPVs may be implicated in the initiation of tumour development but that their continued presence is not necessary for tumour promotion or maintenance, or that the SCC develops via a separate molecular pathway in which HPVs are not implicated, or simply that they are innocent bystanders during oncogenesis. A recent meta-analysis of 17 articles concluded that SCCs were more likely to carry HPV than normal looking skin (pooled effect estimate 3.43, 95% confidence intervals 1.97 to 5.98, $P<0.0001$), although it was somewhat limited by the degree of heterogeneity between the included studies in terms of types of SCC, assays used (broad-spectrum versus limited spectrum polymerase chain reaction, and immunocompetent versus immunosuppressed patients ($I^2=76\%$) (Wang et al., 2014). The mechanisms of the aetiological role of HPVs remain unclear (Harwood and Proby, 2002, Karagas et al., 2006, Bouwes Bavinck et al., 2010)

although further elucidation of these mechanisms could provide exciting prospects for targeted therapies in the future.

1.6 Histopathology

Invasive SCC is characterised by the presence of nests or chords of malignant cells within the dermis and an associated inflammatory infiltrate.

In the 1930's, Broders devised a grading system for SCCs based upon the percentage of differentiated cells present (Broders, 1932), and much of the SCC literature uses this classification:-

- Grade I >75% cells differentiated
- Grade II 50-75% cells differentiated
- Grade III 25-50% cells differentiated
- Grade IV <25% cells differentiated

However, the most recent staging guidelines from the American Joint Committee on Cancer (AJCC7) grade SCCs as 'low-grade' or 'high-grade' without guidance on the percentage of differentiated cells which need to be present to make this distinction (Edge and Compton, 2010). When developing the most recent dataset for the histological reporting of SCC, the Royal College of Pathologists has thus adopted the approach that tumours should be classified as well, moderately or poorly/undifferentiated, based upon appearance of the most poorly differentiated part of the SCC regardless of the percentage of differentiated cells present (Chaudhuri et al., 2006). When assessing differentiation, the degree of keratinisation, the presence or absence of intercellular bridges, the degree of pleomorphism, and the number and type of mitoses are taken into account.

The cells seen in well-differentiated SCCs are typically nucleated with prominent nucleoli and abundant cytoplasm containing tonofibrils and well-developed intercellular bridges (prickles). Pleomorphism is minimal and mitotic figures are uncommon. Keratinisation is often abundant (Figure 8).

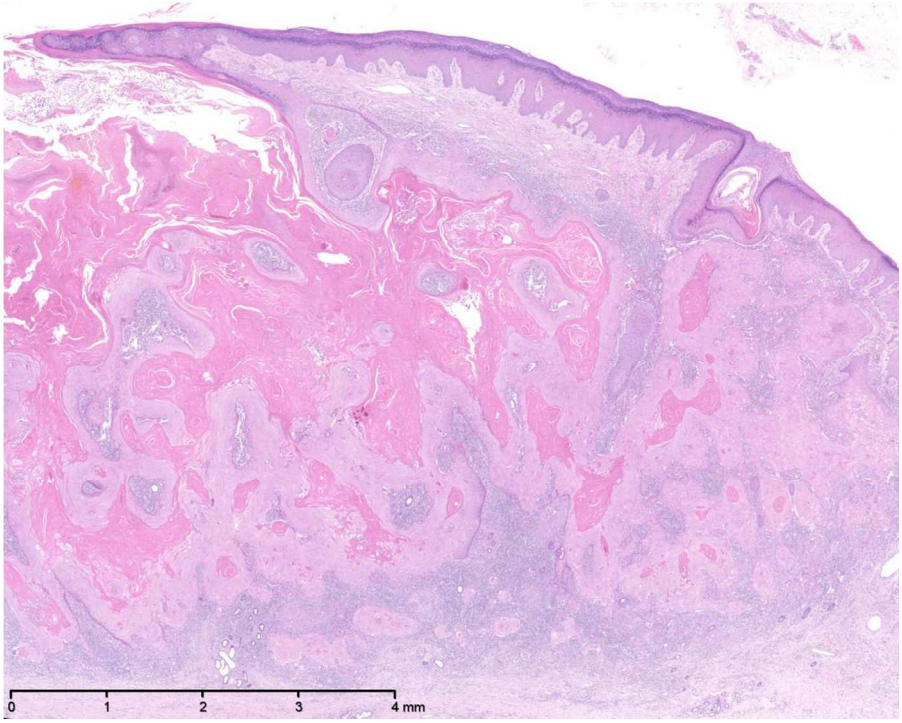


Figure 8: A well-differentiated SCC (image courtesy of Dr I Leach, consultant histopathologist, NUH NHS Trust)

Moderately differentiated SCCs are structurally more disorganised, with cells showing more pronounced nuclear and cytoplasmic polymorphism and more frequent mitotic figures. SCCs that are poorly differentiated have cells with nuclear atypia and frequent mitotic figures and less keratinisation, and may be difficult to definitively diagnose histologically as SCC unless intercellular bridges or small areas of keratinisation are observed (Figure 9).

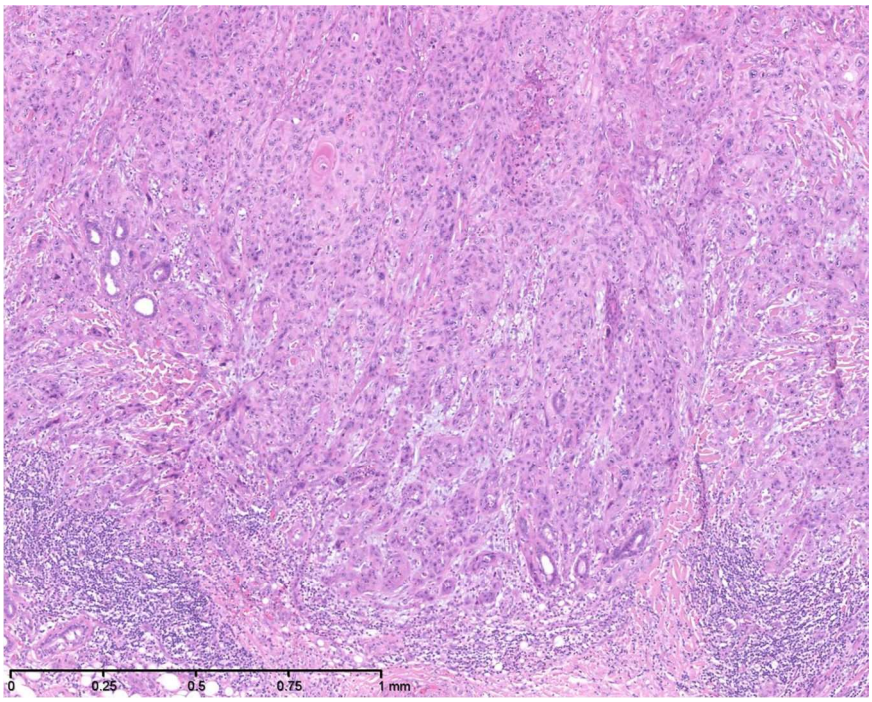


Figure 9: Poorly differentiated SCC with little keratinisation and much nuclear atypia (image courtesy of Dr I Leach)

Rarely cells may be completely anaplastic and give few clues as to the origin of the tumour on microscopy.

Perineural invasion (PNI), defined as 'the observation of cytologically malignant cells in the perineural space of nerves' (Dunn et al., 2009) (Figure 10), occurs in approximately 6% of cases of SCC (Leibovitch et al., 2005b). Such PNI may be 'microscopic' and an incidental finding on routine microscopy in a clinically asymptomatic patient, or 'extensive' in which case the disease is widespread and found either clinically, on radiology, or is apparent at surgery (Han and Ratner, 2007).

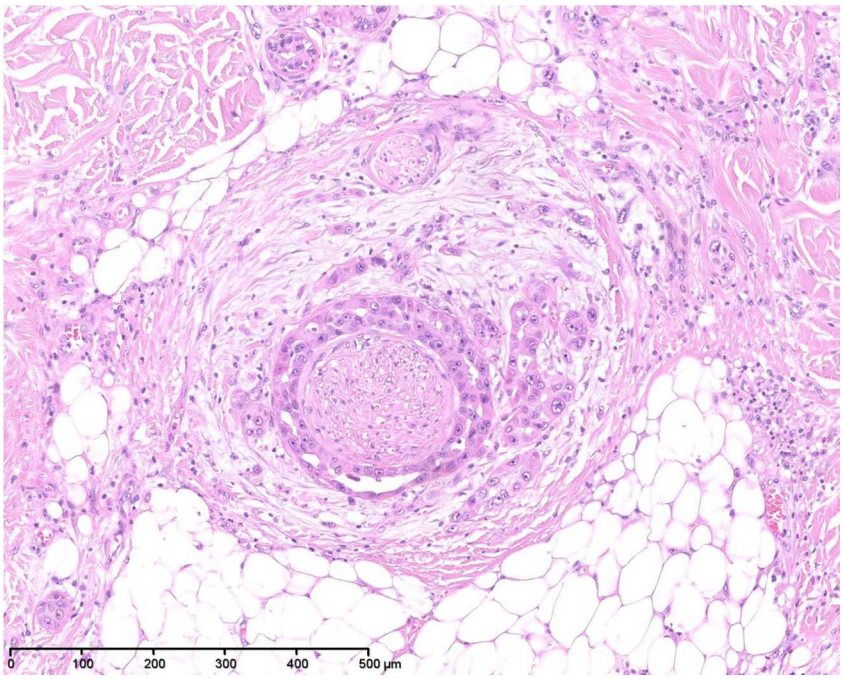


Figure 10: Perineural invasion of 0.25mm calibre nerve (image courtesy of Dr I Leach)

Spread through the perineural sheath offers a low-resistance pathway for extension of tumour that is also relatively protected from the host's defences. Perineural invasion usually extends up to 1cm, although may be much more extensive along cranial nerves with retrograde spread to nerve foramina or the base of the skull and leptomeningeal involvement (Dunn et al., 2009). Studies of SCCs with PNI suggest that they carry a poorer prognosis, particularly for local recurrence (Jambusaria-Pahlajani et al., 2013, Veness et al., 2006, Schmults et al., 2013). A retrospective cohort study of 114 SCCs with PNI suggested that there was greater risk of nodal metastasis (HR 5.6 [95% CI 1.1 to 27.9]) and death from disease (HR 4.5 [95% CI 1.2 to 17] when nerves of calibre greater than 0.1mm were involved compared to involvement of smaller calibre nerves, but this was partly attributed to the association between PNI and other risk factors such as tumour diameter and depth of invasion, so the prognostic significance of nerve diameter currently remains unclear (Carter et al., 2013).

1.7 Pathogenesis

Chronic exposure to ultraviolet radiation, particularly UVB (280-315nm) from sunlight is the major factor in the development of SCC, believed to result from

a chain of events ultimately resulting in DNA damage and mutation formation (Runger, 2007).

Mutations in the *TP53* tumour suppressor gene are the most well-recognised and intensely studied aberrations in the pathogenesis of SCC, being present in more than 90% of SCCs in the United States and in the majority of precancerous lesions, suggesting that alteration of the p53 protein function is an early event towards the development of invasive SCC (Brash, 2006). p53 has a pivotal and complex role in many cellular control mechanisms. In response to its activation by numerous cellular stresses such as DNA damage or hypoxia, p53 is activated, forming tetramers that bind to DNA and activating many genes which results in DNA repair, arrest of the cell cycle and apoptosis (programmed cell death) (Latonen and Laiho, 2005). The gene encoding the p53 protein is located on the short arm of chromosome 17 and is highly conserved (Lamb and Crawford, 1986). A characteristic UVB 'signature' is seen for most of the gene's mutations, with transition of pyrimidine bases, usually cytosine (C) → thymine(T), or CC →TT(Brash et al., 1991). *TP53* mutations are also found in keratinocytes from normal-looking skin in addition to skin showing frank sun-damage, but normal skin turnover may lead to their elimination. However, it has been shown that UV exposure not only produces mutations but can also be a driver of clonal expansion of mutant keratinocytes by the induction of apoptosis of surrounding normal cells, allowing repopulation of the microenvironment by the relatively apoptotic-resistant mutant cells and thus providing an expanded population of abnormal cells for the acquisition of mutations in other driver oncogenes which may then cause progression to invasive SCC (Brash et al., 2005).

The role of UVA (315-400nm) in carcinogenesis is less well understood than that of UVB, and appears to be less mutagenic than UVB and less efficient at producing cyclobutane pyrimidine dimers and pyrimidine-pyrimidine photoproducts. Most UVA damage appears to be indirect through formation of reactive oxygen species and the transfer of energy to DNA via mutagenic oxidative intermediates (Ridley et al., 2009).

Activation or downregulation of other cellular pathways such as those involving epithelial growth factor (EGFR) (Toll et al., 2010, Shimizu et al., 2001) and matrix metallopeptidases (MMPs) (Mitsui et al., 2013) are recognised as having a role in the pathogenesis, maintenance and spread of SCC. Nevertheless, the identification of somatic mutations that drive tumour genesis has remained elusive. Activating mutations of the Ras oncogene are present in low frequency in SCC, and alone may not be sufficient to cause malignant transformation. However, there is concern that Ras-mutation primed cells may render patients treated with RAF inhibitors for BRAF v600E mutation-positive melanoma more susceptible to SCC, although the mechanism of this remains unclear (Oberholzer et al., 2012). Mutations in the genes encoding Notch 1 and Notch 2 receptors, which regulate many aspects of cell development and survival and play a central role in microenvironmental communication, are found in approximately 75% of SCCs and are also a recent source of interest in the search for tumour drivers (Dotto, 2008, Wang et al., 2011). Further elucidation of genetic mutations and their effect on cellular control will continue to be of importance as the search for more targeted therapies for SCC advances.

1.8 Management overview

The aims of treatment of SCC of the skin are to completely remove or destroy the tumour with minimal functional or cosmetic impairment.

A number of treatments are used for SCC and will be outlined briefly below. However, as appraisal of the evidence of the effectiveness of these treatments constitutes a major part of this thesis, outcomes after treatments will be discussed further in chapters 3 and 4.

1.8.1. Surgical Excision

The current treatment of choice for most SCCs of the skin is surgical excision as this allows histological confirmation of complete excision. It is usually carried out as an out-patient procedure under local anaesthetic. The technique involves delineation of clinically obvious tumour either by eye or by curettage, although there is no good evidence that curetting before excision confers any benefit (Chiller et al., 2000). An additional clinically normal appearing margin of skin is excised with clinically apparent tumour, the size of which is based upon the presence of prognostic features and in accordance with current guidelines. Current UK guidelines advise a margin of normal looking skin of 4mm for low-risk tumours, and 6mm for those with high-risk features. These recommendations are based on a single study (Brodland and Zitelli, 1992), in which 95% of SCCs which were excised by Mohs micrographic surgery would have been excised completely with these margins. However, microscopic extension beyond the clinically visible tumour may be more extensive for tumours with poorly delineated clinical borders, tumours larger than 2cm in diameter, and recurrent tumours, so wider margins are more appropriate for tumours such as these (Choo et al., 2005). Indeed, the excision margins recommended in the Australian and US SCC management guidelines are more conservative than those in the UK (Cancer Council Australia and Australian Cancer Network, 2008; National Comprehensive Cancer Network, 2010) with margins up to 10mm recommended. There is therefore no international consensus regarding acceptable margins and no RCTs have been done to address this.

After excision, tissue is either fixed in formalin for histological assessment of completeness of excision, or examined by frozen section. The resulting wound is sutured or allowed to heal by secondary intent, and skin grafting may be necessary if a large tumour is removed or in cosmetically complex areas.

1.8.2. Mohs Micrographic Surgery

Frederick Mohs first developed and described the technique of excision with a micrographically controlled margin when he was a medical student in the

1940s (Mohs, 1947). There have since been refinements and adaptations of the original in vivo zinc paste tissue fixation technique (chemosurgery), although the general principle has remained the same. Essentially the tumour is excised with a narrow margin of clinically normal looking skin and frozen sections are prepared such that the entire margin from the epidermis to the deepest margin can be examined microscopically (usually by the Mohs surgeon who is specially trained in this technique). Margins are marked and mapped, and where residual tumour exists, further tissue is excised. The whole process is repeated until all the margins are clear of tumour so the patient may be in the theatre suite for an entire day and may not be appropriate for those who may not be able to tolerate such a long procedure. As only areas where further tumour is identified are re-excised, the technique tends to be more tissue-sparing than standard surgical excision and is considered to be the gold-standard treatment where tumours are located in areas where cosmetic and functional considerations are important, and also for recurrent tumours and those exhibiting perineural invasion as the technique allows the tumour to be traced along the nerve (Leibovitch et al., 2005b, Lawrence and Cottel, 1994).

1.8.3. Radiotherapy

SCCs of the skin are generally radiosensitive and treatment by this method may be cosmetically and functionally beneficial in certain anatomic locations such as the lip, canthi of the eye, and tip of the nose (Stranc et al 1987). Some sites such as the dorsum of the hand and lower limb are less amenable to radiotherapy, and the use of radiotherapy is best avoided for tumours overlying bones and cartilage where there is the risk of radionecrosis. Its use should also be avoided in younger patients where the late effects from irradiation such as atrophy, hypopigmentation and telangiectases may be cosmetically less acceptable than a surgical scar; furthermore ionising radiation carries with it the small but present risk of development of carcinoma within the treatment field (Karagas et al., 1996). UK management guidelines recommend radiotherapy for tumours which are not resectable or

poorly-defined, with liaison in a multi-disciplinary clinic when there is debate about the best treatment option (Motley et al., 2002).

There is a diverse range of radiotherapy techniques used which are tailored according to tumour characteristics and site, with radiation doses generally being fractionated over a period of weeks to minimise radionecrosis. Generally this involves superficial external irradiation of the tumour and a margin of normal-looking skin, with protection of uninvolved tissue by specially fitted lead masks or shields. Sometimes brachytherapy is used for treatment, with direct application of the radioactive source via interstitial wires or surface moulds, and usually requiring shorter treatment times than conventional radiotherapy.

In addition to the use of radiotherapy as the sole treatment modality for SCC, adjuvant radiotherapy is sometimes used post-operatively, administered either to the tumour-bed alone or to first-echelon lymph nodes, with the aim of eradicating residual tumour cells. It is generally used for tumours considered at high risk of recurrence, and particularly for those that demonstrate PNI or that have been incompletely excised. However, the use of adjuvant radiotherapy varies among clinicians and with the facilities available (personal communication).

1.8.4. Cryotherapy

Cryotherapy employs the use of liquid nitrogen to freeze and destroy cells, usually as two or three cycles with one to five minutes for each cycle, but there is much variation in practice. The diagnosis should be confirmed by biopsy before the procedure, but as with curettage-electrodesiccation, histological confirmation of clearance is not possible. Currently cryosurgery is only recommended for use by experienced practitioners to treat small, well-defined, low-risk tumours (Motley et al., 2002).

1.8.5. Electrodesiccation/cauterisation and curettage

As tumour tissue is usually more friable than surrounding normal tissue, initial curettage of the lesion debulks and helps to delineate extensions of the

tumour, the base of which is then electrodesiccated or cauterised several times to destroy residual tumour, along with a margin of normal looking tissue. The current UK guidelines recommend the use of curettage and electrodesiccation for the treatment of small, well-defined low-risk lesions only, and only then by experienced clinicians. (Motley et al 2002). Furthermore, as with cryotherapy, histological confirmation of complete destruction of the tumour is not possible with this technique.

1.8.6. Photodynamic Therapy (PDT)

In photodynamic therapy a topically applied prodrug, 5-aminolaevulinic acid (ALA) or its methyl ester methylaminolaevulinate (MAL), is converted to the photosensitiser protoporphyrin IX (Pp IX) in the biosynthetic pathway for haem. As haem-containing enzymes are required for energy metabolism, every nucleated cell has the capacity to synthesize PpIX, which is the immediate precursor of haem, although under normal circumstances the pathway is closely regulated so that PpIX does not accumulate to photosensitising concentrations. ALA and MAL selectively accumulate in tumour tissues, possibly as a result of increased permeability of abnormal keratin (Kennedy et al., 1990). Exposure to visible light causes the production of reactive oxygen species which are believed to mediate cell damage, and the inflammatory response and damage to vascular endothelium may also contribute to destruction of tumour cells (Dougherty, 1987).

There have now been RCTs assessing the use of topical PDT for treating NMSCs, in which it has been shown to be effective for the treatment of thin actinic keratoses, Bowens disease and superficial BCCs (Braathen et al., 2007), and it may be considered for treating nodular BCC in situations where surgery may be suboptimal (Morton et al 2008). However, the evidence supporting the use of PDT for treating invasive SCC is very limited.

1.8.7. Other Treatments

Not all SCC patients can be treated surgically or with radiotherapy, and such treatments may also not be appropriate for patients with genodermatoses or

those who are immunosuppressed in whom multiple tumours may be a particular problem. There is currently an unmet need for effective topical and systemic therapies, but as new insights into the molecular pathogenesis of these tumours advances, so does the prospect of new targeted treatments.

The use of treatments such as imiquimod, 5-flurouracil and interferon has largely been restricted to very small case series or case reports of patients with unresectable SCCs and their routine use is not currently recommended (Motley et al 2002). The evidence of the effectiveness of these treatments will be considered in greater depth in chapter 4.

CHAPTER 2:

RATIONALE

2 RATIONALE

2.1 Introduction

There are few people in the United Kingdom who can say that they have not in some way and at some time been affected by a skin condition, either in themselves or in those they care for. Between 23% and 33% of the population are estimated to have a problem with their skin at any one time, and dermatological conditions of all types are the most frequent reason for people to visit their general practitioner. Almost 13 million people in England and Wales consulted their GP with a skin related problem during 2006, and of these 0.8 million (6%) were referred to a specialist (Schofield et al., 2009). The burden of dermatological diseases in today's society cannot be underestimated. Skin cancers form an increasing part of this dermatological burden, and indeed the two most common types of non-melanoma skin cancers, basal cell and squamous cell carcinoma, are the most common cancers in the world. The research presented in this thesis has had, and will have, an impact on the people who are affected by just one of the cancers that can causes such a huge amount of distress and is encountered not only in dermatology but across many specialties: squamous cell carcinoma (SCC).

The SCC research described was just one stream of a wider programme of work, 'Setting Priorities and Reducing Uncertainties for People with Skin Disease' (www.nottingham.ac.uk/research/groups/cebd/projects/nihr-programme-grant.aspx), funded by the National Institute for Health Research (NIHR) under its Programme Grant for Applied Research scheme, and which also included research on eczema prevention and treatment, vitiligo and pyoderma gangrenosum. The overall aim of the programme of work was to set priorities and reduce uncertainties in the prevention and treatment of skin disease using a range of methods, starting with reviews of work already done, identifying research gaps and prioritising these for clinical trials in order to provide answers about uncertainties in the management of these common skin disorders.

This chapter outlines the rationale underpinning this SCC research, the aims and objectives of the PhD, and the role that I have played throughout, with a brief overview of each chapter in order to give insight into the bigger picture.

2.2 Rationale

2.2.1. The burden of squamous cell carcinoma

As discussed in chapter 1, squamous cell carcinoma is a very common cancer in white populations which is particularly prevalent in older people. As average life expectancy increases and the number of older people in society grows, so the number of nonmelanoma skin cancers, including SCC, is set to rise even further. Although the prognosis after treatment is generally good and mortality low, the sheer numbers of SCC means that the burden of morbidity associated with the disease is actually very high. The impact of this morbidity is felt not only by patients and their carers, but by society in general and the healthcare economy particularly (Table 2).

Table 2: Overview of the burden of squamous cell carcinoma

Patients	• Physical cost of cancer itself and its treatment • Associated mortality • Psychological impact • Impact on Quality of Life • Lost days of productivity • Financial costs incurred for care
Carers	• Psychological impact • Financial costs incurred • Lost days of productivity
Society	• Inability to work due to illness or treatment

Economy	• Direct costs of diagnosis and treatment • Indirect cost of lost days • Lost working life years because of premature death

Direct costs to the healthcare system include GP consultations, inpatient admissions, day case treatment and outpatient follow-up. The number of bed-days per year for all types of nonmelanoma skin cancer is double that for melanoma, although this is just the tip of the iceberg as the vast majority of nonmelanoma cancers are treated on an out-patient basis (National Cancer Intelligence Network, 2010). In England in 2002, the estimated total cost of treating skin cancers other than malignant melanoma was more than £71 million, of which nearly £58 million were direct NHS costs and the remainder were indirect costs associated with morbidity and mortality and patient incurred costs (Morris et al., 2005), with the cost of treating each NMSC estimated to be between £889 and £1226 (Vallejo-Torres et al., 2014). These figures are, however, likely to be a significant underestimate in view of problems with capturing activity data for NMSCs. (Morris et al., 2005). With cases of NMSC predicted to continue to rise, the increased burden will have policy implications for medical resources and infrastructure (Fransen et al., 2012); this is a cancer which will continue to have huge cost and resource implications for health services in the United Kingdom and around the world well into the foreseeable future.

2.2.2. Squamous cell carcinoma as a research priority

In 2006, the National Institute for Health and Clinical Excellence (NICE) in its guidance 'Improving outcomes for people with skin cancer including melanoma', highlighted the lack of good-quality research on the effectiveness of treatments for skin cancer and called for studies with long-term follow-up to compare different treatments (Brewster et al., 2007b). An All Party Parliamentary Group on Skin which reported in 2008, also raised concern that

skin cancer had in previous years been afforded a lower priority than it deserved in terms of efforts to prevent it and in planning the services required to manage it, pointing out inadequacies of data collection for skin cancer and calling for more resources to research the cause, prevention and treatment of skin cancer (All Party Parliamentary Group on Skin, 2008).

2.2.3. Why research SCC treatments?

The UK Government has acknowledged the need for more research into all types of skin cancer. As advances are made at bench level to identify molecular aberrations that can result in the development of skin cancer, so the number of potential treatments targeting those aberrations is set to increase. This is an exciting prospect for the future. However, as the already heavy skin cancer workload of busy dermatologists and other clinicians looks set to rise even further, it is important that hitherto unanswered questions about the effectiveness of the current commonly used treatments are first addressed. Patients should have the right to expect a practical and consistent approach to their management based upon the very best evidence available. Yet despite the fact that SCC presents a considerable burden globally, it has been largely overlooked as a distinct type of nonmelanoma cancer which merits being researched in its own right.

For SCC, evidence of the comparative effectiveness of the mainstay treatments recommended in management guidelines has been lacking. It is possible to speculate about why this has been the case. Historically, it may be that all NMSCs were regarded as a single entity to be treated in a similar fashion, and that studies looking at treatments did not separate SCCs from BCCs and other less common types of NMSC. Additionally, there may in the past have been a misconception among both clinicians and the public that these tumours are merely a temporary inconvenience, readily treated and without future implications, and thus that further investigation of well-established treatments was not warranted. SCCs however do not behave in the same way as BCCs; they have different patterns of behaviour and a greater propensity to recur, metastasise and cause death.

There are undoubtedly challenges to conducting high-quality research studies comparing treatment effectiveness for SCCs, not least because they are a very heterogeneous group in terms of both prognostic indicators in the tumours themselves and in the characteristics of the patients affected. Such heterogeneity will need to be taken into account when designing research studies, and should be regarded as an incentive rather than a barrier to conducting such research in that important answers can be addressed about prognostic models and the appropriate targeting of treatment resources.

Conducting prospective studies with long-term follow-up of a condition which is most common in an elderly population, many of whom have other co-morbidities, may also be viewed as a disincentive to this type of research.

However, as the clinical impact of SCC is not set to wane in the near future, and as the elderly population and other susceptible groups such as chronically immunosuppressed continues to grow, this should really be a driving force to spur the development of pragmatic trials whose results are relevant to the people most affected.

2.3 Aim and objectives of this research

All patients who are diagnosed with SCC have the right to receive the optimal treatment for them as an individual which is based upon the best evidence available. This optimal treatment will be satisfactory to them as an individual, giving the best chance of having their tumour completely removed or destroyed whilst minimising the risk of recurrence, metastasis and tumour-related death, and at the same time causing them as little discomfort as possible in terms of quality of life, pain, disfigurement, functional impairment and adverse effects of treatment. With this in mind, the aim and objectives of the research I have been conducting are summarised below.

2.3.1. Aim

To develop a proposal for a well-designed clinical trial that will address areas of management uncertainty for cutaneous SCC and which will help to inform the evidence based management of future SCC patients.

2.3.2. Objectives

- To appraise, summarise and identify gaps in the current evidence-base of the effectiveness of SCC treatments.
- To identify areas of management uncertainty and potential areas for a future trial.
- To assess the feasibility of potential randomised controlled trials (RCTs) through:
    - Evaluation of the number and types of SCCs treated over a one-year period
    - Baseline feasibility work with SCC patients themselves
    - Multi-disciplinary collaboration with clinicians
- To help inform current development of national guidelines of SCC management.
- To develop the proposal and funding application for the randomised clinical trial identified.

2.4 The Research Cycle

I sincerely hope that the first revolution of the research cycle with which I have been involved (Figure 11) will be the first of many more revolutions of the cycle and the start of a much longer journey. I envisage that the findings from the trial which results from this work will help to develop the existing evidence base, generate more questions, and ultimately stimulate further research. Thus the cycle continues.

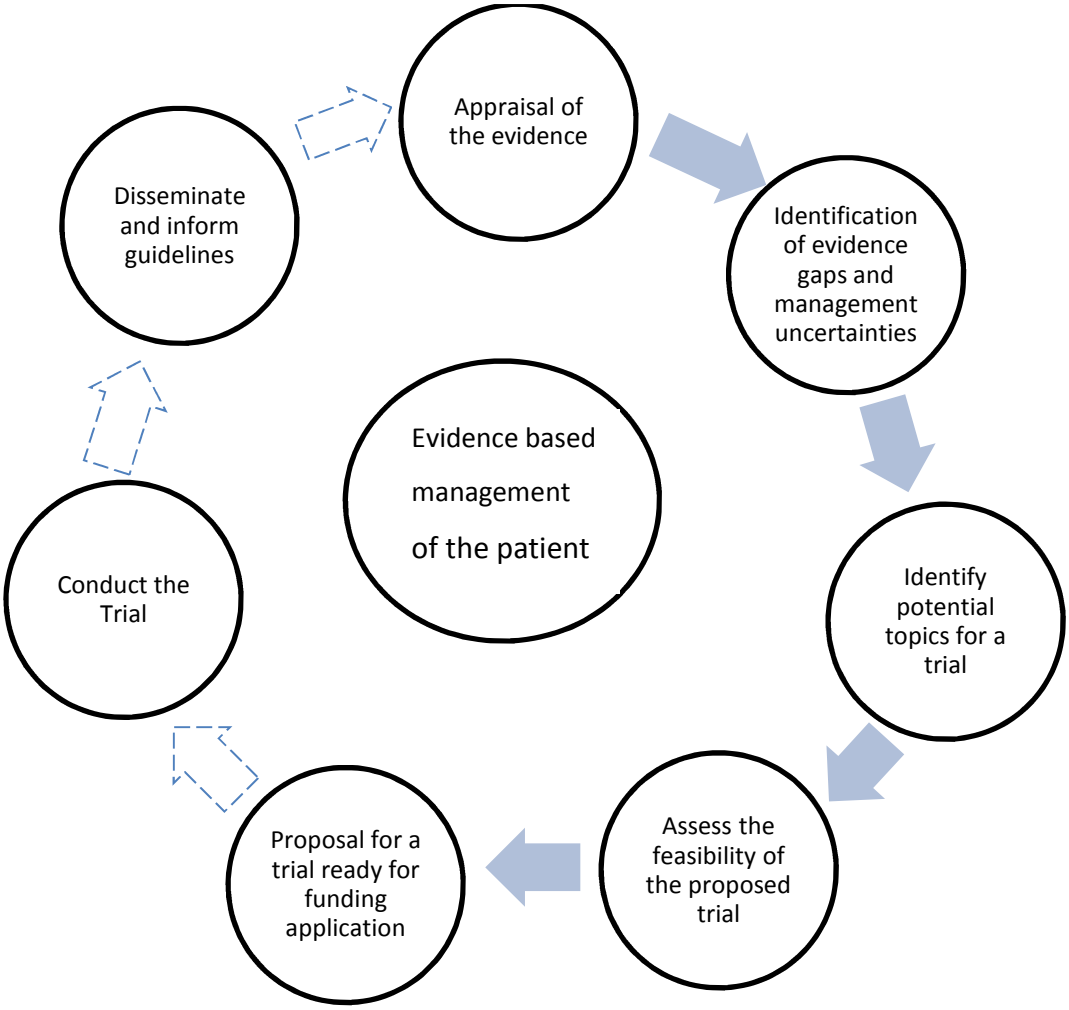


Figure 11: The Research Cycle

2.5 The role that I have played in the research

The research cycle illustrated gives a broad overview of how this work has flowed in order to meet the overall aim of the project and the development of a trial proposal. The work has been made up of a series of individual projects which have linked together and which have each formed a significant piece of research in their own right.

Each piece of work has been done in collaboration with my supervisors and colleagues from various disciplines, and has been overseen as a whole by the NIHR Programme Grant Executive Committee. I have been involved with this research from its beginning, playing a key role in planning and designing each of the specific projects. I have co-ordinated the research, carried out the vast majority of the work, generated ideas, collaborated with colleagues who will

be influential in conducting the definitive trial itself and are involved in the development of management guidelines, and disseminated the results of the work through peer-reviewed articles and presentations at national and international conferences.

A brief summary of subsequent chapters follows, with an outline of my contribution where applicable:

Chapter 3: Appraisal of the Evidence – a Cochrane Systematic Review

The first step on the road to the project's aim was to conduct a Cochrane systematic review which would evaluate the evidence from randomised controlled trials that have compared the effectiveness of different treatments for non-metastatic SCC. The title for this review had previously been registered with the Cochrane Skin Group in 2006 but had not been pursued. It was decided by the Executive Committee that this was a good starting point for the research and needed to be carried forward, so I became lead author on the review, working with the Cochrane Skin Group to develop the search strategies, and working in concert with my supervisors to identify potential titles, source papers for potentially relevant RCTs, and to undertake the double extraction of data. Only one eligible RCT was identified in the review so data analysis was negligible, but I was responsible for drafting the review and responding to referee's comments.

Despite the lack of RCTs, this review has proved an extremely valuable point from which to launch the research; it has highlighted the shocking state of affairs that the second most common cancer has attracted so little in the way of 'gold-standard' research in the past, and emphasises the importance that this situation really need to be redressed, as has been alluded to in the rationale discussed earlier in this introduction.

Chapter 4: Appraisal of the Evidence – a Systematic review of Observational Studies

Following on from the Cochrane systematic review, I decided that it really was necessary to evaluate the current evidence-base more comprehensively by looking at the evidence from non-RCT studies. Only by doing this would information on, for example, event rates and variations in techniques be obtained which would be helpful in planning the trial proposal. The search strategy for this review was designed with assistance of a specialist librarian; I developed the data extraction form myself, and identified potentially relevant studies working in parallel with my supervisors. I extracted all the data from the identified studies, which was also done independently by two other data extractors. As this type of systematic review is quite novel, advice and help with statistical analysis was given by my supervisor, a statistician. I was responsible for interpreting the results and drafting the paper for publication.

Although there are many challenges in conducting this type of systematic review, it would not have been possible to progress the work overall without the information that it has yielded.

Chapter 5: Identification of potential topics for a randomised controlled trial

The poor state of the evidence base for SCC treatments has been shown in chapters 3 and 4. There are many uncertainties that surround the management of this common cancer. Yet what are the questions that clinicians feel are the most pressing and which should be addressed in a trial? In order to answer this, I devised a survey which was sent to clinicians responsible for treating patients with SCC. Colleagues from dermatology, plastic surgery and clinical oncology helped to pilot this and facilitate the survey to be sent to members of their professional organisations. I was responsible for analysing and interpreting the results from the survey.

Chapter 6: Evolution of a trial

Following analysis of the results of the clinician survey, I formulated four scenarios for possible RCTs based upon clinically important management uncertainties identified in the survey. As the success of any SCC RCT trial will

depend upon multidisciplinary collaboration, I presented the scenarios to the National Cancer Research Institute (NCRI) non-melanoma subgroup of the melanoma Clinical Studies group in order to engage with them at an early stage and to facilitate the development of trial proposal. This chapter describes the evolution of the trial from the rationale behind the initial trial scenarios and through their further development.

Chapter 7: Case series of SCCs treated in Nottingham

The Executive Committee overseeing the Programme Grant work specified at the outset that feasibility work needed to be undertaken to inform any proposed trial. This chapter describes the evaluation of SCCs that I considered to be a necessary part of this feasibility work, as it would give information about the numbers of SCCs that are treated in a typical regional centre and the types of SCCs presenting in terms of their prognostic features. After looking initially at these issues for SCCs treated fairly recently, I decided that by extending the evaluation to include SCCs that had been treated 5 years ago it would also be possible to gain information about the number of baseline recurrences, metastases and deaths that occur within 5 years of treatment; information that would be crucial for any future trials. This involved designing a database which could both capture pathological information on SCCs submitted to the histopathology department and clinical outcome data. I designed the key elements of this database, which was constructed and maintained by a colleague with specialist skills in this area. Colleagues in histopathology and dermatology populated the database with information which I then analysed and interpreted.

Chapter 8: Feasibility study with patients

This chapter describes the feasibility study that I decided to conduct in order to evaluate potential participants'' hypothetical willingness to be randomised into the proposed trial, and to examine possible barriers to recruitment which would need to be taken into consideration in the trial design. This work involved a postal questionnaire with open and closed questions, which I

designed myself and piloted with the CEBD patient panel, and a focus group which I organised but which was moderated with my assistance by a qualitative research colleague who has plenty of experience in this role. Data were transcribed, analysed and interpreted by myself using a thematic framework approach.

Chapter 9: The development of the trial proposal

The aim of this PhD has been to develop a proposal for a clinical trial to be taken forward for a funding application. The background work behind this has been described in previous chapters. This chapter outlines how the proposal has evolved to the current trial proposal. The development has been an iterative process, with amendments occurring en route and leading to the proposal as it currently stands and which is to be submitted for a funding application for a full trial. A multidisciplinary approach is crucial in a trial of this nature and as such the involvement of NCRI non-melanoma subgroup of the melanoma CSG is a necessity if the trial is to be successfully funded. I have been involved at every stage as the proposal has developed, having initially presented the trial ideas to the subgroup and taking an active part in all the group's meetings and discussions as the proposal has evolved.

Chapter 10: Impact and conclusions

In the final chapter, I shall summarise the research as a whole, with a discussion of the impact that it is having, how patients have been involved with the research, and its implications for clinical practice and future research. The research cycle that was described in this chapter will be revisited to evaluate how all the research has fitted into the cycle.

This PhD has been a significant part of my life over the past five years. This thesis would therefore not be complete with a personal reflection on the journey that I have trodden and the future one upon which I am yet to embark.

CHAPTER 3:

APPRAISAL OF THE EVIDENCE.

A COCHRANE SYSTEMATIC REVIEW

3 APPRAISAL OF THE EVIDENCE: A COCHRANE SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

3.1 Abstract

Background

Squamous cell carcinoma (SCC) is the second most common skin cancer, and is becoming increasingly common around the world. Left untreated, it may spread to other parts of the body, and, although the risk is low, it may ultimately lead to death. Surgical excision is the first line of treatment for most skin SCCs, although other forms of treatment are also used depending upon the nature and site of the tumour and individual participant factors. A multi-professional approach is therefore required for the management of people with this condition.

Objectives

To assess the effects of treatments for primary non-metastatic squamous cell carcinoma of the skin.

Methods

In February 2010 we searched for relevant trials in The Cochrane Skin Group Specialised Register, *The Cochrane Library* (Issue 1, 2010), MEDLINE, EMBASE, PsycINFO, AMED, LILACS, and the ongoing trials registries.

Only randomised controlled trials (RCTs) of interventions for primary SCC of the skin were included. Participants with one or more histologically proven invasive SCC were eligible for inclusion. The primary outcome measures were time to recurrence one to five years after treatment, and quality of life. Secondary outcomes included early treatment failure within six months, number and type of adverse events by the end of treatment, aesthetic appearance as assessed by the participant and clinician, discomfort to the participant during and after treatment, and death.

Two authors independently carried out study selection and assessment of methodological quality and data extraction.

Main results

Only one trial involving 65 participants met the inclusion criteria, which compared the time to recurrence in participants with aggressive skin SCC who were randomised to receive either adjuvant 13-cis-retinoic acid and interferon alpha after surgery with or without radiation treatment, or no adjuvant therapy after their initial treatment. There was no significant difference in time to recurrence of tumour between the two groups (hazard ratio 1.08, 95% confidence intervals 0.43 to 2.72).

Most studies identified from the searches were excluded as they were either uncontrolled case series, did not include participants with invasive primary SCC, or included only participants with recurrent or metastatic disease.

Conclusions

Very limited evidence exists from RCTs comparing the efficacy of different interventions for primary cutaneous SCCs exists. There is a clear need for well-designed randomised studies in order to improve the evidence base for the management of this condition.

3.2 Introduction

3.2.1. What is evidence-based medicine?

The concept of 'evidence-based medicine' (EBM) is not new and its philosophical origins can be traced back to at least the seventeenth century. However, interest in modern EBM really took off in the 1970s and 1980s and has continued to develop since then (Sackett et al., 1996). One of the founders of modern EBM, David Sackett, defined its practice as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett et al., 1996). Thus good evidence-based practice is a combination of the healthcare practitioner's clinical expertise with the best available external evidence, with the aim of providing the optimal treatment for each patient based on their individual circumstances.

3.2.2. The hierarchy of evidence

Randomised controlled trials and systematic reviews of several RCTs have become the 'gold standard' studies for assessing treatment efficacy, as they are regarded as being most likely to inform and at lowest risk of bias. An example of an evidence hierarchy for studies of treatment effect is shown in Figure 12. There is however, no single universally accepted hierarchy and there has over the years been much debate about the order of study types within hierarchies. For example, Guyatt placed the N-of-1 RCT (a multiple crossover trial in which patients undertake pairs of treatment periods with administration of the target treatments during one period and placebo or alternative treatment during the other) at the top of the hierarchy of strengths of evidence for treatment decisions (Guyatt and Rennie, 2002). Others argue that a single, large well-conducted RCT is preferable to a systematic review and meta-analysis of several smaller studies (Cappelleri et al., 1996).

Figure 12: Hierarchy of evidence for treatment effects. Reproduced with permission from State University of New York Downstate Medical Centre, Medical Research Library of Brooklyn Guide to Research Methods. The Evidence Pyramid. Evidence Based Medicine Course. (http://library.downstate.edu/EBM2/2100.htm (SUNY Downstate Medical Center).

However, hierarchies of evidence have been criticised for their lack of flexibility and simplistic approach to EBM (Smith and Pell, 2003). Indeed, some have called for the abandonment of hierarchies of evidence altogether on the basis that proponents of EBM have deliberately overlooked the methodological limitations of RCTs and meta-analyses:

"In reality, the 'hierarchy of evidence' has done nothing more than glorify the results of imperfect experimental designs on unrepresentative populations in controlled research environments above all other sources of evidence which may be equally valid or far more applicable in given clinical circumstances. The 'hierarchy of evidence' has had no basis whatsoever as a principle of scientific method but has received an almost universal acceptance among biostatistically minded colleagues." (Miles et al., 2000)

When seeking out the best evidence relating to a specific clinical question, it is important to bear in mind that different categories of question are best served by different study designs and that for questions relating to prognosis,

aetiology or diagnostic accuracy, the RCT may not be the most appropriate study design (Petticrew and Roberts, 2003, Guyatt et al., 2000, Glasziou et al., 2004). Case control or cohort studies, for example, are likely to be more useful than RCTs to answer questions about prognosis, aetiology of diseases and harm from treatment, whereas for diagnostic accuracy evaluation cross-sectional studies will be more appropriate than RCTs.

Furthermore, some flexibility is required when considering hierarchies of evidence and it is important to take into consideration the quality of studies when seeking the best evidence; a large well-designed observational study may be more meaningful than a small poorly-designed RCT. Although levels of evidence such as those proposed by the Centre of Evidence-Based Medicine in Oxford (OCEBM Levels of Evidence Working Group, 2011) provide a useful hierarchy of the *likely* best evidence for a range of clinical questions, they do not provide a definitive judgement on the quality of the evidence so it is important that clinicians have essential critical appraisal skills which allow them to interpret the evidence available in a manner which is most meaningful for their own patients.

3.2.3. The role of systematic reviews in evidence based medicine

Systematic reviews and meta-analyses are important steps in the objective application of evidence to patient-centred management, allowing potentially large amounts of information to be assimilated by health care providers, researchers and policymakers. The process of systematic reviewing is formalised and rigorous, following a step-wise process:

- Framing of a clearly focussed research question
- Systematically searching for and retrieving all relevant literature which meets the pre-specified eligibility criteria
- Assessment of the quality of the retrieved literature
- Summarising the evidence, with meta-analysis if appropriate
- Interpretation of the evidence

By using a systematic and explicit methodology, studies with weak design and increased risk of bias can be identified and consistency of results across studies compared, allowing for the systematic interpretation of the data and an assessment of the validity of the findings and the implications for clinical practice and future research. Thus recommendations emanating from systematic reviews are, by virtue of their scientific methodology, more reliable and accurate than the potentially biased personal views of 'experts' conducting traditional reviews but which are not conducted in systematic way.

Meta-analysis, in which statistical methods are used to summarise the results of included studies, may increase the precision of the overall result of a systematic review, with increased power and narrower confidence intervals (Biondi-Zoccai et al., 2011). However, it is certainly not appropriate to carry out a meta-analysis for every systematic review, and there may be too much heterogeneity across included studies in terms of population, intervention, and outcome or study design for meta-analysis to be feasible.

As the systematic review described in this chapter is a Cochrane systematic review which was co-ordinated by the Cochrane Skin Group, the Cochrane Collaboration will be discussed in further detail in subsequent sections. However, it is important to appreciate that not all systematic reviews are quantitative and also that other organisations play an important role in the production of systematic reviews in healthcare. Cochrane reviews are predominantly concerned with systematic reviews of the effectiveness of interventions and diagnostic test accuracy systematic reviews. Systematic reviews of primary research may also be carried out for qualitative studies, with meta-synthesis of evidence as appropriate, and for health economic evaluations. Furthermore systematic reviews may be comprehensive (in which evidence from two or more different types of evidence is considered), overarching umbrella reviews of systematic reviews, or scoping reviews in which the research question is generally very broad and the purpose of the review is to map the existing literature and identify gaps without focussing

greatly on the quality of the individual studies. The Joanna Briggs Institute (JBI)(http://joannabriggs.org/) is an example of a body that works closely with the Cochrane Collaboration to produce systematic reviews that would generally not be in the remit of the Cochrane group. Established in 1996 by the Royal Adelaide Hospital and University of Adelaide and with more than 70 collaborating centres worldwide, the strength of the JBI lies particularly in the development and conduct of systematic reviews of qualitative, economic and policy research to support and promote the translation of research evidence into practice globally. In the field of education, criminal justice, social policy and social care, the Campbell Collaboration (http://www.campbellcollaboration.org/) is Cochrane's sibling organisation with close affiliation between the two in recognition that social interventions are also relevant in the wider field of healthcare. Additionally, systematic reviews are also conducted under the auspices of other organisations such as the National Institute for Health and Care Excellence (NICE) in the UK, and the Agency for Healthcare Research and Quality (AHRC) in the United States.

3.2.4. Cochrane systematic reviews

In 1972 Archie Cochrane (Figure 13), a physician and significant contributor to the development of epidemiology as a scientific discipline, published his book "*Effectiveness and Efficiency: Random Reflections of Health Services*", in which he strongly advocated using evidence from RCTs to make medicine more efficient and effective (Cochrane, 1972). His subsequent challenge to the medical profession to critically evaluate the evidence from RCTs, was a spur for the development of the systematic review:

*"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials." (*Cochrane*,* 1979*)*

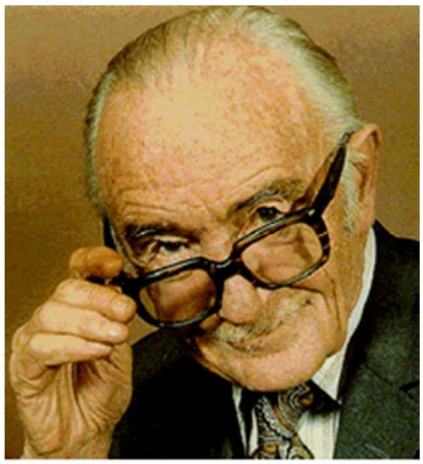


Figure 13: Archie Cochrane, after whom the Cochrane Collaboration is named (image courtesy of Cardiff University Library, Cochrane Archive, University Hospital Llangough)

The first Cochrane Centre opened in Oxford in 1992, followed by the foundation of the Cochrane Collaboration in 1993 under the leadership of Sir Iain Chalmers who was strongly influenced by the writings of Archie Cochrane.

Figure 14: Logo of the Cochrane Collaboration

The Cochrane Collaboration (Figure 14) is a not-for-profit independent worldwide network of health practitioners, researchers and patient advocates which has the aim of promoting evidence-based health decision making through the production and publication of readily accessible high-quality and up-to-date systematic reviews and meta-analyses.

Cochrane reviews are systematic reviews that are carried out according to the methodology of the Cochrane Collaboration as set out in the Cochrane Handbook (Higgins and Green, 2011), and which are included in the Cochrane Library (available at www.thecochranelibrary.com/). Cochrane reviews have

been regarded as the benchmark for systematic reviews as they are generally considered to be methodologically rigorous, less prone to bias, better reported and more frequently updated than non-Cochrane systematic reviews published in peer-reviewed journals (Egger et al., 1997, Jadad et al., 1998, Jadad et al., 2000).

3.2.5. Risk of Bias assessment

Interpretation of the data in a systematic review depends upon whether the results of included studies are internally valid; in other words, that the results are a fair reflection of the truth and that the study is free from systematic errors, or biases, that could lead to either an under- or over-estimation of effect size. Many tools and scales have been used to assess the quality of RCTs included in systematic reviews (Moher et al., 1995, Moher et al., 1996), although many of these also included assessment of the reporting and methodological quality of studies rather than focussing on methodological flaws which could introduce bias, which may be considered to be separate issues. The Cochrane Collaboration places emphasis on assessing the degree to which potential sources of bias have been avoided in individual studies by evaluation of the risk of bias using a domain-based risk of bias tool (Table 3), as even studies which are conducted to the highest possible standard may still have significant biases if they are methodologically flawed (Higgins and Green, 2011)

Table 3: Potential sources of bias in RCTs and domains in the Cochrane Collaboration's Risk of Bias tool which address these (Higgins and Green, 2011)

Source of Bias	Domain in risk of bias tool
Selection (systematic differences between baseline characteristics in the comparator groups)	**Sequence generation** (was the sequence allocation adequately generated? e.g. random number generator, coin tossing) **Allocation concealment** (could the

	assignment have been foreseen?)
Performance (systematic difference between the groups in the care provided)	**Blinding** of participants, trial personnel and outcome assessors (were measures taken to prevent participants, trial personnel and outcome assessors having knowledge of which intervention was allocated?)
Attrition (systematic differences in study withdrawals between the groups)	**Incomplete outcome data** (were incomplete outcome data addressed adequately?) **Blinding** of participants, trial personnel and outcome assessors
Detection (systematic differences in outcome determination between the groups)	**Blinding** of participants, trial personnel and outcome assessors
Reporting (systematic differences between reported and unreported findings)	**Selective outcome reporting** (were expected and pre-specified primary and secondary outcomes addressed?)

3.2.6. The Cochrane Skin Group

First registered in 1997, the Cochrane Skin Group (www.skin.cochrane.org) is one of 53 Cochrane collaborative review groups whose aim is to produce the best possible evidence on the effectiveness of healthcare interventions for people with skin problems by the production and updating of reviews of trials relating to skin conditions.

The title for this Cochrane systematic review was registered with the Cochrane Skin Group, who assisted with design of the search strategies and the editorial process. The protocol for the review was published in the Cochrane Library prior to publication of the final review (Lansbury et al., 2009).

3.2.7. Why it was important to do this review

The burden of SCC to both individuals and to the healthcare system is only likely to grow due to the increased proportion of elderly people in the population. More than 80% of NMSCs occur in people aged 60 years and older, and with an increasingly ageing population, a 50% increase in NMSC workload for UK dermatologists by 2030 has been predicted (Watson and Torgerson, 2006). Consequently, a consistent and practical approach to the management of SCC will become imperative in future years.

A variety of treatment methods have been used in the management of SCC, although there has previously appeared to be a paucity of large randomised trials that have compared their effectiveness. Several case series have reported the common treatment modalities (Rowe et al., 1992) and current SCC management guidelines are largely based on evidence from these (Motley et al., 2002). There have, however, been no systematic reviews previously conducted in this area and management guidelines have been largely based on evidence from treatment of other types of NMSC and case series. The Cochrane systematic review described in this chapter was a starting point from which to identify any RCTS that had been done in the field, to appraise the current evidence base of the effectiveness of different

treatments from any identified RCTs, to identify where more evidence appraisal is required, and to help direct researchers towards future research requirements.

3.2.8. Objective of the review

The objective of this review was to assess the evidence available from RCTs for the effectiveness of treatments used in the management of cutaneous SCC.

3.3 Methods

Details of the search strategies for this review may be found in Appendix 1. MeSH and text words were developed and searched based on the condition and interventions, and filters developed by the Cochrane Collaboration were used to identify RCTs.

3.3.1. Types of studies

Published and unpublished RCTs comparing treatments for primary non-metastatic, invasive SCC were eligible for inclusion in the review. Observational studies were not included, and these will be discussed separately in chapter 4 of this thesis.

3.3.2. Types of Participants

Randomised controlled trials were eligible for inclusion in the review if they included participants of either sex who had one or more histologically proven primary non-metastatic SCC and who were eligible to be randomised to either active treatment, placebo or other treatment. Studies which had only participants with Bowen's disease and/or actinic keratosis or only immunosuppressed participants were excluded. Participants were not included if they had persistent (i.e. a number of treatments had been tried without success), recurrent or metastatic SCCs. Non-cutaneous SCCs (head and neck, lung, gastro-intestinal, urinary tract and genital) were also excluded as these sites require special interventions and a different approach.

3.3.3. Types of interventions

Interventions included:

- Surgery
    - Excisional surgery
    - Mohs micrographic surgery
- Destructive treatments
    - Curettage and cautery or electrodesiccation
    - Cryosurgery
    - Photodynamic therapy

- Laser therapy
- Radiotherapy

- Other interventions
  - Topical therapy e.g. imiquimod, 5-fluorouracil
  - Intralesional treatments e.g. interferon
  - Chemotherapy.

Adjuvant treatments in combination with any of the above treatments were also included. Complementary therapies were not addressed in this review.

3.3.4. Outcomes

Primary outcomes of interest were:

a) Recurrence (time-to-event), one to five years after treatment, measured clinically at the site of the original tumour, or at the local lymph nodes, or distant metastasis, after apparently successful initial treatment
b) quality-of-life.

Secondary outcomes of interest were:

a) early treatment failure within 6 months confirmed histologically;
b) number of adverse events by the end of treatment;
c) cosmetic appearance as assessed by i) the participant, or ii) the clinician;
d) discomfort to the participant during and after treatment; and
e) death.

3.3.5. Search methods for identification of studies

An electronic search was performed for relevant published trials in the following databases:

- The Cochrane Skin Group Specialised Register;
- Cochrane Central Register of Controlled Trials (Clinical Trials) in *The Cochrane Library;*

- MEDLINE (from 2005 to 11 February 2010);
- EMBASE (from 2007 to February 2010);
- PsycINFO from inception;
- AMED (Allied and Complementary Medicine) from inception;
- LILACS (Latin American and Caribbean Health Science Information database) from inception.

In addition I searched the following trials registers for ongoing trials:

- the metaRegister of Controlled Trials (www.controlledtrials.com);
- the US National Institutes of Health ongoing trials registry (www.clinicaltrials.gov);
- the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organisation International Clinical Trials Registry platform (www.who.int/trialsearch);
- the Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Bibliographies of published studies and key review articles were scanned for possible references to randomised controlled trials.

Attempts were made to find unpublished studies through correspondence with key authors publishing in the area.

There were no language restrictions imposed and studies were translated into English if necessary.

3.3.6. Data collection

Two reviewers checked the titles and abstracts identified from the searches, and independently assessed the full text of potentially relevant studies to decide if they met the inclusion criteria. Studies were excluded if it was clear that they were not RCTs comparing treatments for cutaneous SCC. If it was unclear whether this was the case then the full paper was obtained for independent assessment. Any disagreements were resolved by discussion and

a consensus decision was made. If data was missing from potentially relevant reports, the trial author was contacted to try to obtain the data.

Data for each study were independently extracted by two reviewers, with resolution of discrepancies by a third reviewer. Data were checked and entered into RevMan.

3.3.7. Risk of Bias assessment

A risk of bias assessment was done according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) based on the following components:

- the method of generation of the randomisation sequence;
- method of allocation concealment;
- blinding of participants, clinicians and outcome assessors;
- loss of participants to follow-up in each arm and if analysis was on an intention-to-treat basis

The following were also assessed:

- the degree of certainty that participants had SCC; and
- baseline comparison of the study arms in terms of disease severity.

The results were summarised in a Risk of Bias table.

3.3.8. Data analysis

Time-to-event outcomes were expressed as hazard ratios (HR) with 95% confidence intervals.

The log hazard ratio and its variance was estimated using a Microsoft Excel spreadsheet authored by Matthew Sydes (Cancer Division) in collaboration with the Meta-Analysis Group of the MRC Clinical Trials Unit, London, which is based on Parmar's methods (Parmar et al., 1998).

The unit of analysis was randomised participants rather than lesions.

In the protocol for the full review, an intention-to-treat analysis would have been conducted if participant drop-out lead to missing data, with the last

recorded value carried forward for participants with missing continuous outcome data, and for dichotomous outcomes, participants with no recorded data would be regarded as treatment failures and included in the analysis.

3.4 Results

3.4.1. Search results

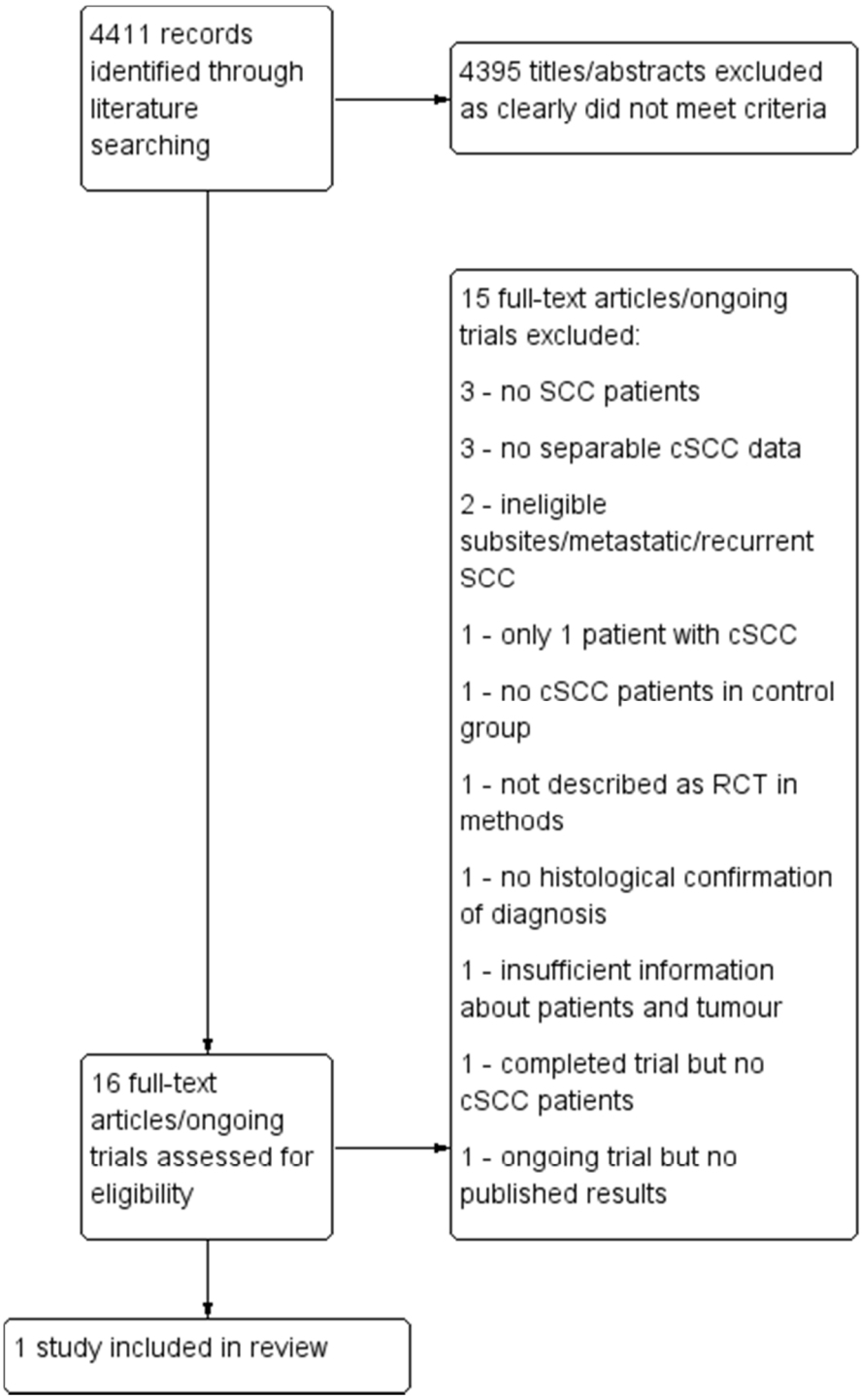


Figure 15: Flowchart of studies in the review

The results of the literature search are summarised in Figure 15. From a total of 14 studies assessed at full text and 2 ongoing trials, only one study was eligible for inclusion in the review (Brewster et al., 2007a).

3.4.2. Included study

Characteristics of Included Study

The included RCT (Brewster et al., 2007a) was a single-centre, parallel-group study from the USA which included 65 evaluable male and female patients with pathologically-confirmed aggressive skin SCC. The primary outcome was time to tumour recurrence or development of a second primary tumour. A total of 31 participants received adjuvant 13-cis-retinoic acid and interferon alpha after surgical treatment, whereas the 34 participants in the control arm received no adjuvant chemotherapy after primary surgical treatment.

Characteristics of the included study are shown in Table 4.

Table 4: Characteristics of included study (Brewster et al., 2007a)

Methods	Single Centre Design: Parallel
Participants	Tertiary care, USA Randomised: 66 (1 withdrew consent immediately after randomisation) Evaluable: 65 61 males, 4 females Age range 34-81 years Pathologically confirmed aggressive skin SCC exhibiting one of following: size ≥2cm diameter; perineural invasion; deep invasion of muscle, cartilage or bone or fixation to these; proven regional metastases.
Interventions	T1: Adjuvant therapy with 13-cis -retinoic acid (1mg/kg/d orally) and Interferon alpha (3 x 10^6U subcutaneously 3 times weekly) for 6 consecutive months after surgery or radiation therapy. T2: No adjuvant therapy after surgery or radiation therapy
Outcomes	Follow up: complete physical and skin examinations at 3,6,18 and 24 months post-randomisation Primary end point: Time to tumour recurrence or development of a second primary tumour. Secondary end point: quantitative and qualitative toxicity during 6 months of 13cRA and IFN-α therapy
Notes	7 patients discontinued prematurely: 1 withdrew consent immediately after randomisation; 3 lost to follow-up at 7,12 and 18 months; 2 patients died after cardiac arrest (1 in treatment group 5 months after completing treatment, and 1 in observation group); 1 patient in intervention group dropped out because of adverse events after 1 week of adjuvant therapy.

Risk of Bias in the Included study

Assessment of the risk of bias is summarised in Figure 16.

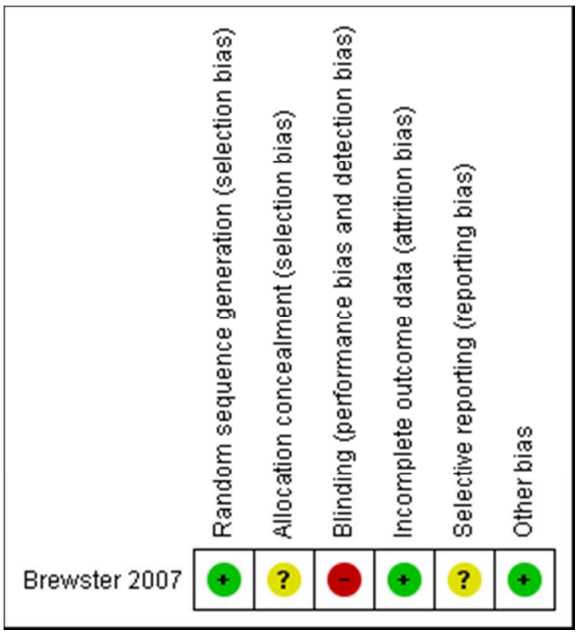


Figure 16: Diagrammatic representation of risk of bias assessment for included study (Brewster et al., 2007a)

The randomisation method was described as 'permuted block randomisation within strata' but details about the adequacy of concealment of allocation were not available. Neither clinicians nor participants were blinded to allocation due to the nature of the intervention. Analysis of the primary outcome was carried out on all evaluable participants apart from one who withdrew consent immediately after randomisation. Histological confirmation of SCC was obtained for all participants, and there were no clinically relevant or demographic baseline differences between participants in each trial arm.

Effects of interventions

Primary outcomes

Time to recurrence

In the one included study, no statistically significant difference in the time to recurrence was seen between participants who received adjuvant chemotherapy and those who did not, HR 1.08, 95% CI 0.43 to 2.72 (Figure 17).

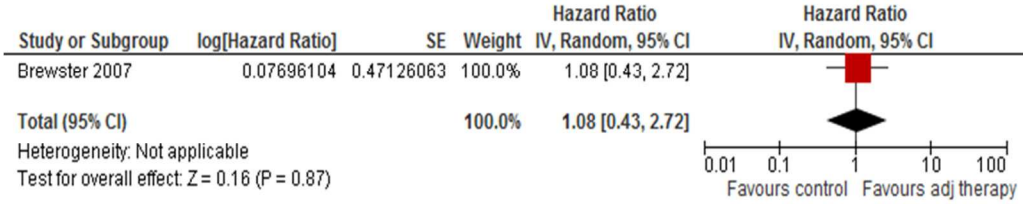


Figure 17: Forest plot comparing time to recurrence between 13-cis-retinoic acid plus interferon alpha treatment arm and control arm

Quality of life

The included trial did not compare QoL between the treatment and control arm participants.

Secondary outcomes

Adverse events

The most frequently reported adverse events among participants in the treatment arm of the included trial were dry skin, fatigue and generalised lip and eye reactions. However, a total number of adverse events could not be determined, as it was possible that participants may have experienced more than one adverse event each.

Death

No treatment-related deaths were reported in the included trial. There were two non-treatment-related deaths during follow-up, one in the treatment arm and one in the control arm.

No data were available for the other secondary outcomes of early treatment failure, aesthetic appearance, and discomfort to participants.

3.4.3. Excluded and Ongoing Studies

Thirteen articles, of which 11 were fully published and 2 were abstracts, were excluded from the review (Brandt et al, 2007, Cham et al, 1991, Coates et al, 1984, Haas et al., 1976, Healy, 1969, Landthaler and Braun-Falco, 1989, Lui et al., 2004, Moseley et al, 1976, Medical Research Council, 1976, Perez et al., 1991, Seyss, 1968, Eedy, 2003, Radny et al, 2006).

Two other trials were also identified, one had just been completed but was excluded as there were no participants with cutaneous SCC (CHARTWEL trial) (http://clinicaltrials.gov/show/NCT00021125). No published results were available at the time from the other ongoing trial (TROG 05.01) which is comparing post-operative chemo-radiotherapy (carboplatin) with post-operative radiotherapy alone for high-risk advanced primary or nodal cutaneous SCC of the head and neck to improve loco-regional relapse. (www.who.int/trialsearch/trial.aspx?trialid=ACTRN12607000146493). At the time of writing this study is still recruiting with estimated study completion in late 2018.

Characteristics of Excluded Studies

Fourteen potentially eligible RCTs were excluded from the review. Three studies were excluded as there were no participants with invasive SCC (Lui et al., 2004, Eedy, 2003, Seyss, 1968), and a further three as there was no specific cutaneous SCC data (Brandt et al, 2007, Coates et al, 1984, Haas et al., 1976). The remaining studies were excluded for the following reasons: SCC diagnosis was not confirmed histologically and there was no data on the distribution of SCCs in the intervention and control groups (Healy, 1969); SCCs were located only on ineligible subsites (Medical Research Council, 1976); all SCCs were recurrent or metastatic (Perez et al., 1991); only one eligible participant had cutaneous SCC (Moseley et al 1976); there were no

participants with cutaneous SCC in the control group (Cham et al, 1991); it was not possible to determine from the full-text if the study was randomised (Landthaler and Braun-Falco, 1989); no information was provided about included participants and tumours (Radny et al, 2006).

3.5 Discussion

3.5.1. Summary of the evidence

Only one RCT met the inclusion criteria for this systematic review (Brewster et al., 2007a). However, the risk of bias in the included study was unclear across several of the domains assessed (Figure 16). The included study compared a group of patients who received adjuvant treatment with 13-cis-retinoic acid plus interferon alfa with a group who did not have adjuvant treatment after initial surgery and/or radiotherapy. There were 65 participants, with no statistically significant difference between the two groups in terms of time to recurrence or time to development of second primary tumour. The tumours included in the study were, by definition, high-risk, aggressive tumours with a very high risk of an event during the first two years after initial treatment. The study may have been underpowered to detect a significant difference between the two groups given the wide confidence intervals around the hazard ratio, and the trial authors acknowledged that this may limit interpretation of their results, highlighting the difficulty of accruing a sufficient number of patients with the aggressive types of SCCs which were being evaluated in the trial, even from a tertiary centre.

A large number of potential studies were retrieved in the database search. However, the majority could not be considered for inclusion in the review, as they were either uncontrolled case series (Chapter 4), or they were RCTs which only included BCCs or non-invasive SCCs such as actinic keratosis or Bowen's disease.

3.5.2. Completeness and applicability of the evidence

This review highlights the paucity of RCT data relating to the management of non-metastatic cutaneous SCC. Furthermore, the only prospective trials that have been or are being conducted to date, have addressed the most aggressive and high-risk types of SCC, rather than those which are considered to be lower risk. It may be that the perception of cutaneous SCC as a relatively innocuous tumour which can be easily treated by surgical excision has led to

the smallest and lowest-risk tumours being largely ignored in prospective trials and given a low research priority. Nonetheless, if the same argument were applied to the most common form of NMSC, BCC, one would similarly expect to see few RCTs for this tumour; this is not the case and there is no shortage of RCTs comparing treatment modalities for BCC (Bath-Hextall et al., 2007).

On the other hand, it may be that the more aggressive nature of SCCs and their propensity to recur and metastasise may result in a reluctance among researchers to randomise participants to novel treatment arms on ethical grounds. Also, even though SCC is a common tumour, it displays much heterogeneity in terms of prognostic features and for the results of a trial to be externally valid and relevant to people with similar types of SCCs, tumour characteristics should be taken into account when designing trials. Therefore the number of eligible SCCs may be limited, and accruing sufficient numbers of participants to ensure that the study is adequately powered to detect a significant difference between treatments could be challenging and require a multi-centre approach.

The review has therefore highlighted the lack of evidence from RCTs regarding the effectiveness of treatments for non-metastatic SCCs and those that are less aggressive than the cases assessed in the included trial. It is, however, the less aggressive SCCs that are most commonly seen in clinical practice, and for which the evidence base for treatments is currently lacking.

3.5.3. Potential biases in the review process

The systematic literature search and contact with leading experts on the field of SCC managements makes it unlikely that eligible RCTs have been missed.

Meta-analysis was not possible in this review as there was only one eligible RCT included.

3.5.4. Agreement and disagreements with other studies or reviews

This is the first systematic review that has attempted to assess the evidence from RCTs for interventions for non-metastatic SCC. Current guidelines on SCC management are based largely on the evidence from case series (Motley et al., 2002), and appraisal of this evidence will be discussed in chapter 4 of this thesis.

3.5.5. Implications for clinical practice

Due to the lack of RCTs, coupled with the limitations (including small sample size) in the one included trial, it was not possible to make specific recommendations for clinical practice from this review.

3.5.6. Implications for research

Invasive SCC is a common NMSC, yet its management has not been investigated in the form of rigorous RCTs to the same extent as BCC or intra-epithelial neoplasia. Gaps in the evidence base which may be usefully investigated by future RCTs are discussed later in this thesis (chapters 4 and 5). However, the shocking lack of RCTs revealed in this review has highlighted an overwhelming need for well-designed randomised studies to compare treatment modalities for primary SCC in order to provide high-quality evidence upon which to base clinical decision- making. Below are some suggestions for items which should be considered when designing future trials:

- Primary invasive SCCs should be studied separately from other types of nonmelanoma skin cancers and non-invasive tumours.
- Standardised outcome measures would improve consistency across studies and make their findings easier to compare.
- Outcomes which should be assessed include 5-year recurrence, quality of life, safety and tolerability profiles, cosmetic appearance, and cost implications.

- Tumour prognostic features such as diameter, depth, histology and site should be taken into consideration when designing trials and analysing the results.
- Studies should be adequately powered and multicentre trials undertaken if accrual rates are likely to be low.
- The management of the patient with SCC may be multidisciplinary, so collaboration between specialities should be encouraged.

The management of people at particularly high risk of developing SCC, such as those who are immunosuppressed or with a predisposing genetic condition, has not been addressed in this review. It is, however, an important issue, and an area worthy of separate review.

This Cochrane systematic review only included RCTs. However, it is important to consider the evidence from study types that are lower in the evidence hierarchy than RCTs if the current evidence-base of the effectiveness of treatments is to be fully appraised and to be of use in guiding future clinical practice and research and in the development of a trial proposal. Therefore, the next chapter will describe a second systematic review that has been conducted as part of this research addressing the evidence from observational studies, which contribute to the overwhelming majority of the evidence for primary cutaneous SCC.

CHAPTER 4:

APPRAISAL OF THE EVIDENCE. A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

4 APPRAISAL OF THE EVIDENCE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

4.1 Abstract

Objectives: To assess the effects of treatments for non-metastatic invasive cutaneous squamous cell carcinoma using evidence from observational studies, given the paucity of evidence from randomised controlled trials (RCTs), in order to help focus the research question for a future RCT of SCC treatments.

Design Systematic review of observational studies.

Data sources Medline, Embase, to December 2012 and bibliographies of published studies.

Eligibility criteria Observational studies of interventions for primary non-metastatic invasive cutaneous SCC in which recurrence during follow-up, quality of life, initial response to treatment, adverse events, cosmetic appearance, or death from disease were reported. Studies were excluded if data for primary cutaneous SCC was not separable from other data.

Data extraction and analysis Data were extracted independently by two reviewers. Meta-analysis was performed where appropriate using a random effects model to estimate the pooled proportion of an event with 95% confidence intervals.

Results 118 publications were included covering seven treatment modalities. Pooled estimates of recurrence were lowest after cryotherapy, and curettage and electrodesiccation (0.8% [95% CI 0.1-2.2; 8 studies], and 1.7% [95% CI 0.5-3.4; 7 studies]) respectively, but the majority of treated SCCs treated were small, low-risk lesions. Following Mohs micrographic surgery, the pooled estimate of local recurrence during variable follow-up periods from 10 studies was 3.0% (95% CI 2.2-3.9), lower than the pooled average local recurrence of 5.2% (95%CI 2.5-9.1) for standard surgical excision (12 studies), and 6.4% (95% CI 3.0-11.0) following external radiotherapy (7 studies), although as the

confidence intervals overlap these differences were not statistically significant. After an apparently successful initial response to photodynamic therapy, the pooled average recurrence of 26.4% (95% CI 12.3-43.7) (8 studies) was relatively high. Evidence was limited for laser treatment (1 study), and topical and systemic treatments (mostly single case reports or small non-comparative series with limited follow-up).

Conclusions A large number of observational studies have been published that look at many different treatment modalities, but the evidence base for the effectiveness of interventions is poor. Comparison of outcomes after different treatment modalities has to be interpreted cautiously due to biases inherent in the types of study included and lack of head-to-head comparisons to enable the estimation of relative treatment effect.

4.2 Introduction

4.2.1. Why it was important to do this review

The Cochrane systematic review described in chapter 3 has highlighted that RCTs that compare the effectiveness of different treatments for cutaneous squamous cell carcinoma (SCC) simply do not exist. Nonetheless, whilst searching for RCTs it was apparent that there have been many observational studies published which describe outcomes after treatment of SCC, and that these are overwhelmingly case series. Indeed, current management guidelines for SCC are based predominantly on the evidence from such studies (Motley et al., 2002). However, observational studies reporting SCC treatment outcomes have not previously been reviewed systematically following the principles of systematic reviewing outlined in the previous chapter of this thesis.

Whilst recognising that observational studies are subject to inherent biases which will be discussed shortly, there is also much useful information that can be obtained from them, particularly in an area like this where there are so many uncertainties. It was therefore vital to systematically assess these studies, not only to have a wider overview of the SCC treatment evidence base as it currently stands, but more importantly to provide background quantitative and qualitative data that will allow for better planning of a randomised controlled trial, such as information about outcome event rates and standardisation of interventional techniques .

As the vast majority of studies included in this systematic review were case series, with a small number of case reports for more anecdotal treatments, the discussion in this section will focus mainly on case series.

4.2.2. Definition of a case series

A case series is a descriptive study in which a group of patients who have received a similar intervention are followed over a period of time. There is no appropriate comparison group.

4.2.3. Limitations of case series

A key problem with case series is that they lack a comparator group and so are inherently prone to bias Table 5. Consequently the lack of a comparison group may make it seem as though there is an association between an intervention and outcome, when this may not necessarily be the case, and causal inferences should not be drawn from case series regarding the relationship between a treatment and an outcome (Kooistra et al., 2009).

Table 5: Potential sources of bias in case series

Potential bias	Possible reasons for bias
Selection bias	○ Patients in series not representative of the general population e.g. selected on the basis of the likelihood of response to intervention ○ Non-consecutive patients. ○ Retrospective design may decrease completeness of inclusion, data collection and follow-up.
Performance bias	○ Patients in series treated differently in some way from others e.g. extra visits. ○ Lack of blinding.
Detection bias	○ Outcomes assessed to favour intervention ○ Lack of blinding.
Reporting bias	○ Only patients with favourable outcomes reported ○ Lack of blinding
Survival bias	○ Some patients may not be reported as having died or did not return for follow-up due to treatment failure or success. ○ Incomplete follow-up data.
Publication bias	○ Favourable outcomes more likely to be reported and published than those that are negative.
Confounding	○ A systematic influence beyond the treatment may influence the outcome but cannot be adjusted for in the absence of a control group.

Unlike RCTs, most case series have no published protocol and are not subject to the same quality control measures as RCTs, which may make them more susceptible to data manipulation and fraud (Albrecht and Bigby, 2008).

4.2.4. Strengths of case series

Case series and reports are often regarded as the least methodologically robust study designs for reasons mentioned above, although well-designed and reported case series do have a place in furthering medical knowledge (Kempen, 2011, Kooistra et al., 2009, Black, 1996).

In the absence of RCTs, it may be that the only evidence available is from case series. There are some circumstances in which it would be considered inappropriate to conduct an RCT to establish the effectiveness of a treatment, for example for 'all-or-nothing' interventions such as insulin for type 1 diabetes in which all patients would die without administration of the drug, or the use of penicillin for group A streptococcal infections. Additionally, for a treatment that is already considered to be clearly effective and accepted into practice, it may be very difficult to get funding to conduct an RCT to compare it with an alternative treatment, although if the evidence upon which such treatments are based is weak then their effectiveness really should be questioned. The effectiveness and safety of many 'accepted' interventions has been refuted after an RCT was finally conducted, an example being the use of dexamethasone in patients with cerebral malaria which was introduced into practice in the 1960s but which was subsequently shown to be deleterious in these patients (Warrell et al., 1982). Furthermore, ethical considerations may preclude randomisation of patients with particular diseases to non-treatment arms, and sometimes it is practically unfeasible to recruit a sufficient number of participants to adequately power RCTs evaluating treatment of rare diseases or those in which outcomes are infrequent, very long-term and for interventions with rare adverse events. The first indication of rare adverse events or rare outcomes may therefore come from case series.

Although causal inferences should not be deduced from case series, they may provide the initial information that is required in order to generate a hypothesis that can be tested further through more formalised experimental designs.

A major perceived advantage of case series over RCTs is their higher external validity, particularly if they include a diverse range of patients who are not subject to the often rigorous inclusion and exclusion criteria laid out in explanatory RCTs, which aim to measure the efficacy of a treatment under ideal conditions and often use carefully defined subjects. Explanatory RCTs are in contrast to pragmatic RCTs which assess the effectiveness of treatments in routine clinical practice and reflect the variations between patients that occur in real clinical practice with the aim of informing choices between treatments. However, case series may be favoured by some clinicians as they are less costly and quicker than RCTs, with clinicians and patients retaining control over decisions made about treatment (Kooistra et al., 2009, Audige et al., 2006, Hartz and Marsh, 2003).

Ultimately, the value of a case series, as with all study designs, will depend upon the quality of its design and the steps that have been taken to minimise bias when possible, in addition to the quality of the report itself which will enable healthcare practitioners to judge whether the patients in the series are comparable with their own patients.

4.2.5. Assessing the quality and risk of bias in case series

Lack of planning, incomplete or inconsistent data collection (for example, information about prognostic factors) and poor reporting of key diagnostic and therapeutic details can severely compromise the validity of non-randomised studies (Ergina et al., 2009).

A key component of any systematic review and meta-analysis is an assessment of the limitations of the primary studies contained within it, regardless of the studies' design, in order that a fair interpretation of the results may be made. There is a distinction between methodological quality,

risk of bias and the quality of reporting of the study, and strength or weakness in one of these components is not necessarily reflected in the others. For example, a well-executed study may nonetheless have design flaws which put it at high risk of bias. Similarly a study may theoretically be at low risk-of bias by virtue of its design, but if it is poorly reported the reader may not have adequate information to make an informed decision about this (Huwiler-Muntener et al., 2002).

There are many tools that have been proposed for assessing the quality and risk of bias in studies that are included in systematic reviews, including scales, checklists and domain-based evaluations. Many, such as the Jadad score (Jadad et al., 1996), Delphi list (Verhagen et al., 1998) and Megens-Harris list (Megens and Harris, 1998) have been designed specifically to appraise controlled trials. Between 2005 and 2007, collaboration between methodologists, editors and systematic review authors under the auspices of the Cochrane Collaboration led to the development of the Cochrane Risk of Bias tool (Higgins and Green, 2011) which is now well-validated. However, less attention has been paid to the quality and risk of bias assessment for observational studies that are included in systematic reviews, and this is an area where further development is still required. A Health Technology Assessment found little evidence to support the use of many of the criteria included in the quality assessment tools they assessed, although none of the tools they examined were designed specifically for case series or appeared to be evidence based. It called for further investigation of the relationship between methodological features of case series and outcomes in view of the frequency with which case series were being used in Health Technology Assessments (Dalziel et al., 2005). In an evaluation of non-randomised intervention studies, Deeks et al (Deeks et al., 2003) identified 194 tools to assess non-randomised studies, although most were poorly developed and omitted key quality domains. Six tools were identified as potentially useful for assessing quality of non-randomised studies in systematic reviews but all required revision. In a more recent systematic review, Sanderson et al

reviewed 86 tools for assessing quality in observational studies, of which 41 were checklists, 12 were checklists with additional summary judgement, and 33 were scales (Sanderson et al., 2007). There was a lot of variation between the number and nature of items, but the review highlighted that there is no one obvious single tool for assessing the quality of observational studies and that such tools should be rigorously developed, valid, easy to use and focus on the assessment of sources of bias.

Tools are currently being developed for assessing non-randomised studies which are based on the Cochrane Collaboration's domain-based Risk of Bias assessment, which are showing moderate reliability, and acceptable feasibility and validity, although they require further validation and refinement (Kim et al., 2013, Palmer et al., 2011). Some of the authors developing these tools would, however, argue that in areas where the quality of studies is regarded as being low, the added time and complexity of assessing the risk of bias may not be worthwhile (MacLennan et al., 2011).

The tools that are already in existence or under development are generally applicable to non- applicable to non-randomised study designs that do have a control group and they have not been they have not been designed to evaluate case series, for which there are currently no validated currently no validated quality and risk of bias assessment tools. Therefore, in the absence of a the absence of a suitable tool, the assessment of study quality and risk of bias in this systematic in this systematic review is based upon the Cochrane risk of bias assessment tool (Higgins and Green, tool (Higgins and Green, 2011) which has been modified for the purpose of this review, together with this review, together with a tool based upon suggestions drawn up by Joerg Albrecht for improving Albrecht for improving the quality of case series (Williams et al., 2008)(

Table 6 and Table 7). As some of Albrecht's criteria relate more to the quality with which the study was reported rather than specifically the risk of bias, for example they do not address survival bias and information bias relating to unblinded outcome assessment, the two tools are used together in this review. Albrecht's criteria are based on a few published articles (Moses, 1984, Abel, 1999, Jenicek, 2001) and on Albrecht's own experience of systematic

reviews and ethical considerations of case series and reports (Albrecht et al., 2009a).

These are not validated assessment tools for the purpose of systematically reviewing of case series, and were used in the absence of any more suitable tool.

Of importance to note is that assessment of quality of case series can be severely hampered by poor reporting (Dalziel et al., 2005). In 2007 a group of researchers, methodologists and editors developed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement which aimed to establish a checklist of items that should be included in reports of observational studies (Vandenbroucke et al., 2007). This is not intended as a tool by which the quality of the research should be evaluated, but as adherence to its principles is now required by the editors of many leading medical journals, it should make the assessment of quality of observational research a somewhat easier task in the future.

4.2.6. Objective of this systematic review

The objective of this review was to assess the evidence for SCC treatments available from studies other than RCTs, in order to help plan for a future trial addressing the management of cutaneous SCC, to feed into management guidelines, and to stimulate further research in the field.

Table 6: Checklist for quality assessment for case series and case reports, based on Albrecht's criteria (Albrecht et al., 2009b)

Diagnosis	**Are diagnostic criteria clearly identified and met by patients in the case series?**
Inclusion and exclusion criteria	Are inclusion and exclusion criteria clearly stated? Selection bias
Informed consent	Has patient consent been documented? For prospective studies, has ethical approval been documented?
Consecutive cases	Are all consecutive cases treated by one clinician or at one institution included? Selection bias by reporting selected cases.
Natural course of the disease	Is there any reference to the natural course of the disease, or, if applicable the course on standard treatment?
Dosages	Are the dosage, duration and titration of the treatment adequately described so that they are reproducible?
Outcome measures	Are the outcomes of the treatment well defined and clinically relevant?
Patient perception	Is there any documentation of the patient's perception of the outcome of treatment?
Safety	Do the authors describe known risks associated with the intervention?
Authors' conclusions	Do the authors abstain from making unfounded claims about safety and efficacy?

Table 7: Modified risk of bias tool for this systematic review (based on (Higgins and Green, 2011)

Domain	Description
Blinding (Yes/No/Unclear)	Were outcome assessors blinded?
Incomplete outcome data (Yes/No/Unclear)	Were attrition and exclusions adequately describes and addressed ?Survival bias
Other potential sources of bias – retrospective versus prospective design (Yes/No/Unclear)	Was the study retrospective? ?Selection bias if not all eligible patients included

4.3 Methods

The systematic review was conducted according to the MOOSE guidance for meta-analysis of observational studies (Stroup et al., 2000). Details of the protocol for this systematic review were registered on the PROSPERO database (International Register of Systematic Reviews) and can be accessed at www.crd.york.ac.uk/Prospero/display_record.asp?ID=CRD42011001450.

4.3.1. Types of studies

All studies other than RCTS were eligible for inclusion if they reported surgical excision, Mohs micrographic surgery, radiotherapy (external radiotherapy, brachytherapy and adjuvant radiotherapy), laser irradiation, photodynamic therapy, cryotherapy, curettage and electrodesiccation, topical treatments (5-fluorouracil and imiquimod), or other chemotherapy as treatment of previously untreated invasive cutaneous SCC, which was non-metastatic at presentation.

4.3.2. Types of participants

Studies were eligible for inclusion if they included participants of either sex who had one or more histologically proven primary non-metastatic invasive SCC. Participants with Bowen's disease and/or actinic keratosis only were not eligible for inclusion in the data analysis. Participants were not included if they had persistent SCC (i.e. a number of treatments had been tried without success, or their SCC was recurrent and/or metastatic). Non-cutaneous SCCs, including head and neck, mucosal, lung, gastrointestinal urinary tract and genital SCCs, were also excluded from this review.

4.3.3. Types of interventions

- Surgery
    - Excisional surgery
    - Mohs micrographic surgery
- Destructive treatments
    - Curettage and cautery or electrodesiccation

- Cryosurgery
- Photodynamic therapy
- Laser therapy
- Radiotherapy
  - External radiotherapy
  - Brachytherapy
  - Adjuvant radiotherapy after initial treatment

- Other interventions
  - Topical therapy e.g. imiquimod, 5-fluorouracil
  - Intralesional treatments e.g. interferon
  - Chemotherapy
  - Other adjuvant therapies

4.3.4. Outcomes

Primary outcomes of interest, based upon those in the Cochrane systematic review, were :

a) Recurrence during follow-up from 1 month to 10 years after apparently successful treatment, recorded as being at the site of the original tumour (local recurrence), or to the regional lymph nodes (regional recurrence), to distant organs (distant metastases), or unspecified recurrence.
b) Quality-of-life

Secondary outcomes of interest were:

c) Initial response to treatment
d) Cosmetic appearance of treated area
e) Adverse events related to treatment
f) Death due to disease

4.3.5. Search strategies

The MEDLINE (1948 onwards) and EMBASE (1980 onwards) databases were searched to December 2012 for relevant studies using search criteria for

observational studies based on Scottish Intercollegiate Guideline Network (SIGN) filters (http://www.sign.ac.uk/methodology/filters.html#obs). The bibliographies of included studies and recent review articles were also checked for additional articles which were relevant. Due to the large number of studies and limited accuracy of translation, only studies published in English were retrieved.

4.3.6. Study Selection and data extraction

Three review authors independently checked the titles and/or abstracts of studies that potentially met the inclusion criteria. Studies which clearly did not refer to treatment of SCC of the skin were excluded. The full-text was obtained for those studies that potentially fulfilled the inclusion criteria or for which the scope was unclear. Any disagreements were resolved through discussion between the authors.

Studies were excluded if it was not possible to extract data for primary non metastatic SCC, for example, those containing data for mixed populations of SCC and BCCs, previously treated and untreated SCCs, or primary and metastatic SCCs. Studies in which separate data were not reported for different treatment modalities were also excluded. Due to the large number of studies, studies reporting outcomes after surgical excision and Mohs micrographic surgery were only included if there were 20 or more eligible participants, unless they were restricted to a specific anatomical location, such as periorbital or auricular.

Data were extracted independently by two reviewers and entered onto a standardised, pre-piloted data extraction form for assessment of study quality and evidence synthesis. A third author resolved any discrepancies.

4.3.7. Quality of reporting and Risk of Bias

As discussed in the introduction, the quality of the reporting of each study was evaluated , using a self-developed tool based on criteria suggested by Albrecht for reporting case series and case reports (Williams et al., 2008) and

on a modified Cochrane Risk of Bias table (Higgins and Green, 2011). Case series and open-label studies were scored for the number of reporting quality items present and arbitrarily rated as being of poor (score 0-3), intermediate (4-7) or good quality (8-10).

For those studies in which pharmaceutical preparations were an integral part of the treatment modality, we also recorded the declaration of sponsorship by a pharmaceutical manufacturer.

4.3.8. Data analysis

For each study, raw proportions were calculated using the number of events divided by the total number of people in the study. The variances of the raw proportions were stabilised using the Freeman-Tukey variant of the arcsine square root transformation (Stuart and Ord, 1994). Pooled analyses were conducted on the transformed quantity using a random effect model, to allow for heterogeneity resulting from inherent biases within the studies. Analyses were conducted using StatsDirect Version 2. There was no accepted cut-off for the I statistic, as it has been argued by Julian Higgins that any level of heterogeneity is acceptable, provided that the predefined eligibility criteria for the meta-analysis are sound and that the data are correct (Higgins, 2008). As there were tight predefined eligibility criteria and recommended methods were used to ensure the data were correct, it was therefore felt appropriate to present the results from the meta-analysis as this gives crucial information regarding likely recurrence across treatments.

It was not possible to directly allow for differences in length of follow-up using time-to-event as an outcome measure due to lack of such data in the papers. However, when possible, subgroup analysis was performed with comparison of the outcomes in those studies in which the mean follow-up was given as less than 2 years, between 2 and 5 years, and greater than 5 years.

To examine the effect of removing studies with greatest potential for risk of bias, a sensitivity analysis was conducted where possible by repeating the analysis with data from selected papers meeting at least three of the following criteria: 50 or more SCCs reported; mean follow-up greater than 3 years; recurrence type specified; scoring 8–10 on the reporting quality assessment.

Adverse events and cosmetic appearance outcomes were described qualitatively.

4.4 Results

4.4.1. Studies included in this review

The searches identified 3826 publications after removal of duplicates, of which 451 were potentially eligible based on their titles; on review of the abstracts 161 records were not relevant to the review. Two hundred and ninety full-text articles were assessed for eligibility, of which 172 were excluded, mainly due to lack of separable primary SCC data, leaving 118 which were included in the review (Figure 18). There were 106 non-comparative studies, and 12 single case reports, which were included due to a lack of more robust study designs for particular interventions. Four studies reported outcomes for more than one treatment modality. (Full details of the studies, including details of the methodology, types of SCC included, and quality of reporting are included in the supplemental appendix of the published paper (Lansbury et al., 2013).

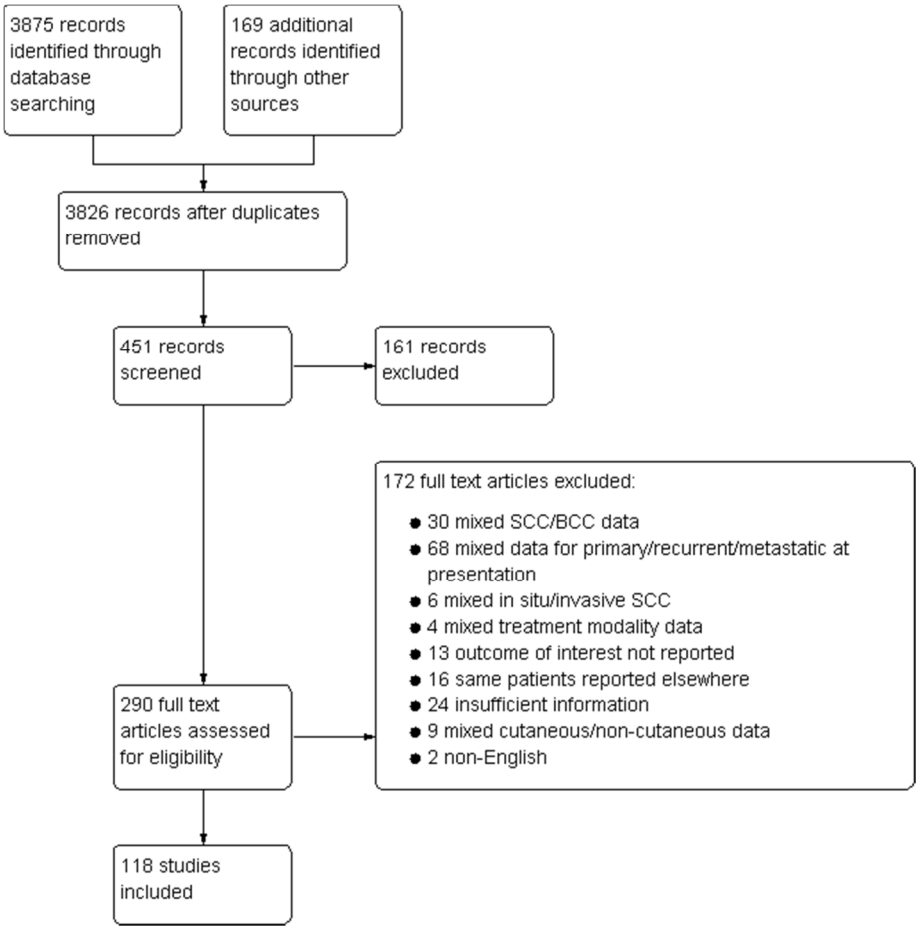


Figure 18: Flow chart of studies

4.4.2. Risk of Bias in the included studies

A summary of the risk of bias for the studies is presented in Figure 19.

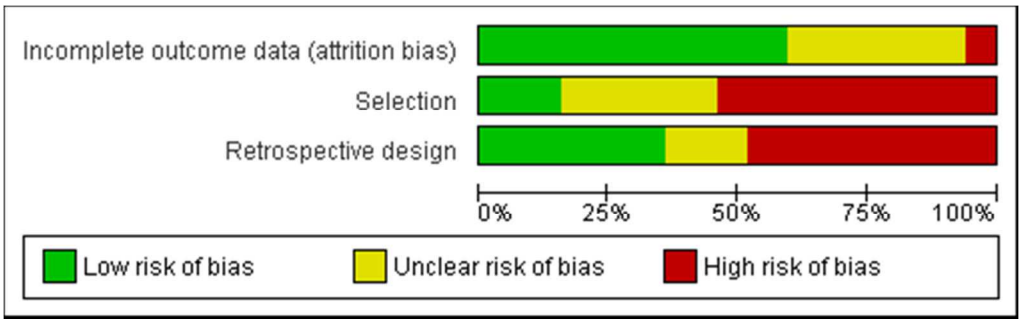


Figure 19: Risk of Bias assessment in the included studies

Forty-eight per cent of studies were evaluated as having a retrospective design, and 36% as prospective; the remaining studies could not be evaluated with regard to the design due to the lack of sufficient information reported in the publications. Overall, 41% of studies were assessed as being at high or unclear risk of attrition bias due to analyses not accounting for losses to follow-up. Selection of a specific treatment modality on the basis of tumour or patient characteristics was assessed as presenting a high risk of bias in 54% of the studies, with low risk in 15%. Risk of bias relating to selection could not be assessed in the remaining 31% of included studies due to insufficient reporting in the publications.

There was no blinding of outcome assessors in any of the included studies.

Overall 13% of the case series were classified as being of poor reporting quality, 56% as intermediate quality, and 30% as high quality. Of 24 studies in which topical or systemic treatments were reported, 7 (29%) received some form of sponsorship from a pharmaceutical company but did not declare that the sponsor had had no involvement in the design, results and analysis of the study.

4.4.3. Surgical excision

There were 12 included studies (1144 patients). Local recurrence during follow-up after surgical excision ranged from 0% to 15% (Baker et al., 2001, Rank, 1973, Donaldson et al., 2002, van der Eerden et al., 2010, Nemet et al., 2006, Reifler and Hornblass, 1986, Shiu et al., 1980, Thomas and Matthews, 1994, Fitzpatrick and Harwood, 1985, Shiffman, 1975, Griffiths et al., 2002, Pless, 1976), with an estimated overall pooled recurrence of 5.4% (95% CI 2.5 to 9.1, I^2=81%) (Figure 20).

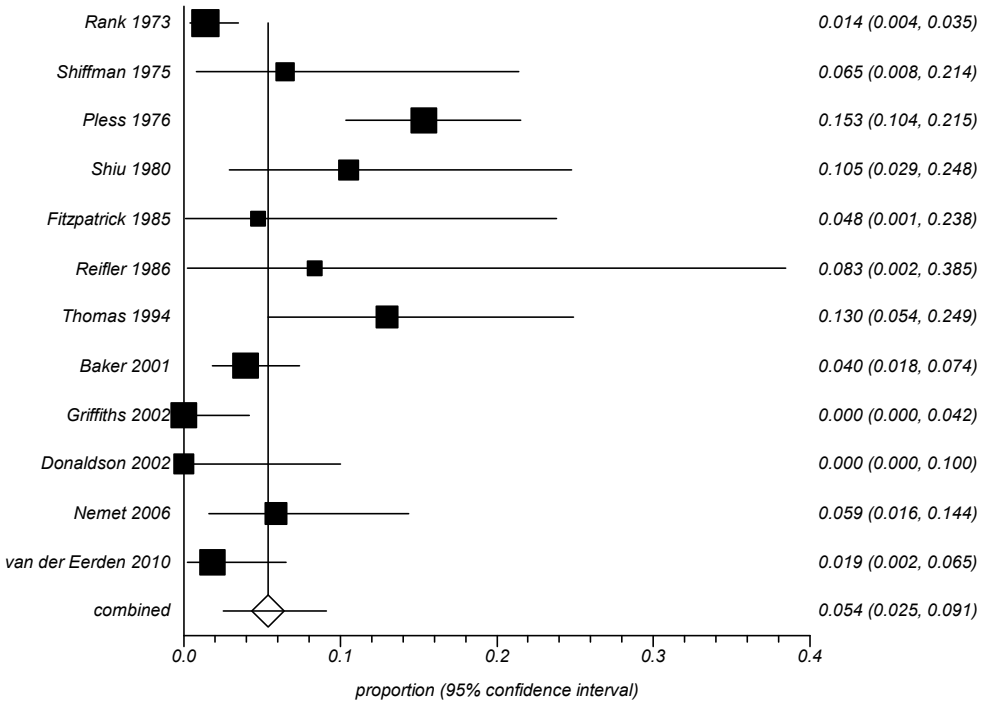


Figure 20: Surgical excision - local recurrence proportion meta-analysis plot [random effects]

Duration of follow-up varied between the studies. One study had a mean follow-up period of less than 2 years (16 months) with local recurrence of 1.8% of surgically excised SCCs of the head and neck region (van der Eerden et al., 2010). In those studies with mean follow-up of between 2 and 5 years (736 patients), recurrence ranged from 0% to 13.0%, with a pooled estimate of recurrence of 5.0% (95% CI 2.3 to 8.3, I^2=62%)(Donaldson et al., 2002, Rank, 1973, Baker et al., 2001, Nemet et al., 2006, Reifler and Hornblass, 1986, Thomas and Matthews, 1994, Fitzpatrick and Harwood, 1985, Shiffman,

1975). One of the 12 studies had a minimum follow-up period of 5 years and reported no local recurrences of 86 surgically excised SCCs at various sites (Griffiths et al., 2002). Three studies reported recurrence of 4.8% for eyelid SCCs (Fitzpatrick and Harwood, 1985), 10.5% for trunk and extremity SCCs (Shiu et al., 1980), and 15.3% for SCCs of the pinna (Pless, 1976) but did not specify for how long patients were followed.

SCCs located in the ear region were associated with highest recurrence rates. Three studies (N=261) in which SCCs of the pinna were surgically excised gave a pooled average local recurrence of 14.1% (95% CI 10.2 to 18.5, I^2=0%) (Thomas and Matthews, 1994, Shiffman, 1975, Pless, 1976) , compared with a significantly lower pooled average of 3.2% (95% CI 1.5 to 5.5, I^2=57%) for the nine studies (N=916) in which SCCs at other sites were included (Figure 21 and Figure 22) (Baker et al., 2001, Rank, 1973, Donaldson et al., 2002, van der Eerden et al., 2010, Nemet et al., 2006, Reifler and Hornblass, 1986, Shiu et al., 1980, Fitzpatrick and Harwood, 1985, Griffiths et al., 2002).

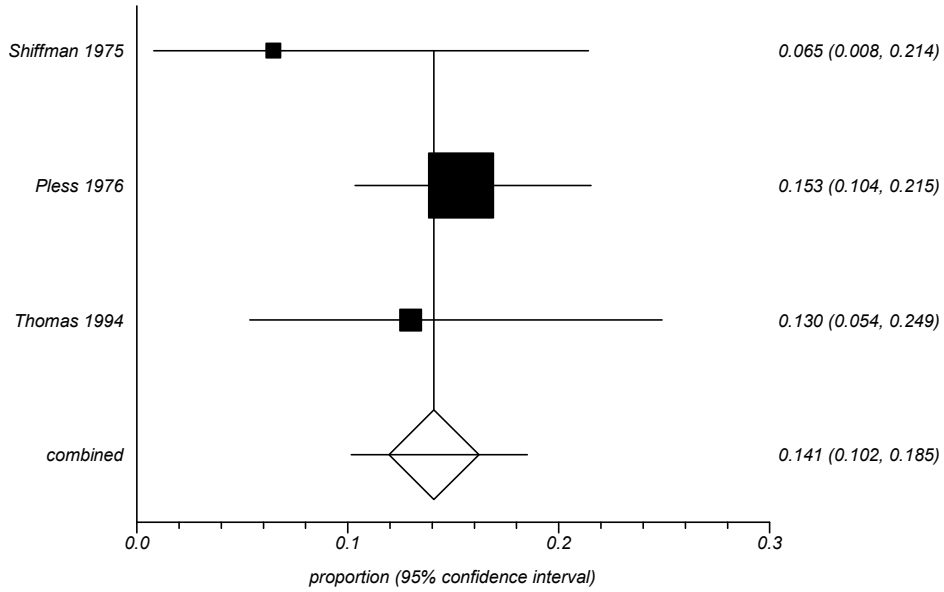


Figure 21: Surgical excision local recurrence ear location proportion meta-analysis plot [random effects]

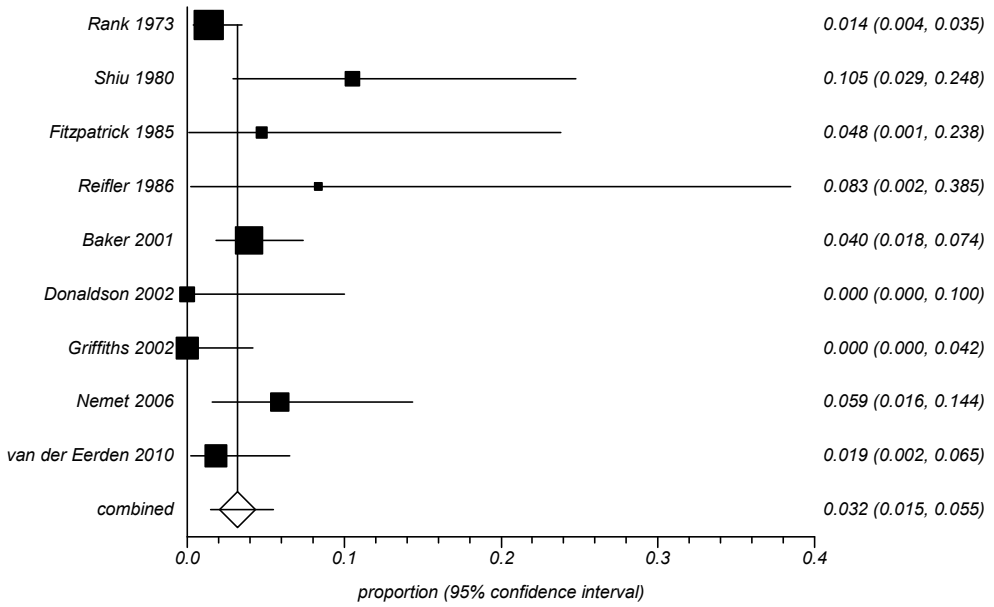


Figure 22: Surgical excision local recurrence non-ear location proportion meta-analysis plot [random effects]

A non-significant tendency for increased local recurrence with increasing SCC diameter was noted in one series, with local recurrences in 12.2% (95% CI 4.6 to 24.7) of the 49 lesions smaller than 10mm in diameter, 14.3% (95% CI 7.8 to 23.2) of the 91 lesions 10–30mm in diameter, 21.7% (95% CI 7.4 to 43.7) of 23 lesions 30–40mm in diameter, and 42.8% (95%CI 9.9 to 81.6) of the 7 tumours greater than 40mm in diameter (Pless, 1976).

Sensitivity analysis of the four papers meeting the criteria for studies at lowest risk of bias had no significant effect on local recurrence (4.2% [95% CI 0.6 to 10.8, I^2 81.4%]) (Thomas and Matthews, 1994, Nemet et al., 2006, van der Eerden et al., 2010, Griffiths et al., 2002).

Recurrence in regional lymph nodes after surgical excision of SCC was reported in eight series (comprising of 786 patients), ranging from 0% to 9.7% (Reifler and Hornblass, 1986, Donaldson et al., 2002, van der Eerden et al., 2010, Baker et al., 2001, Thomas and Matthews, 1994, Pless, 1976, Mourouzis et al., 2009), with pooled average recurrence of 4.4% (95% CI 2.4 to 6.9, I^2=50%)(Figure 23).

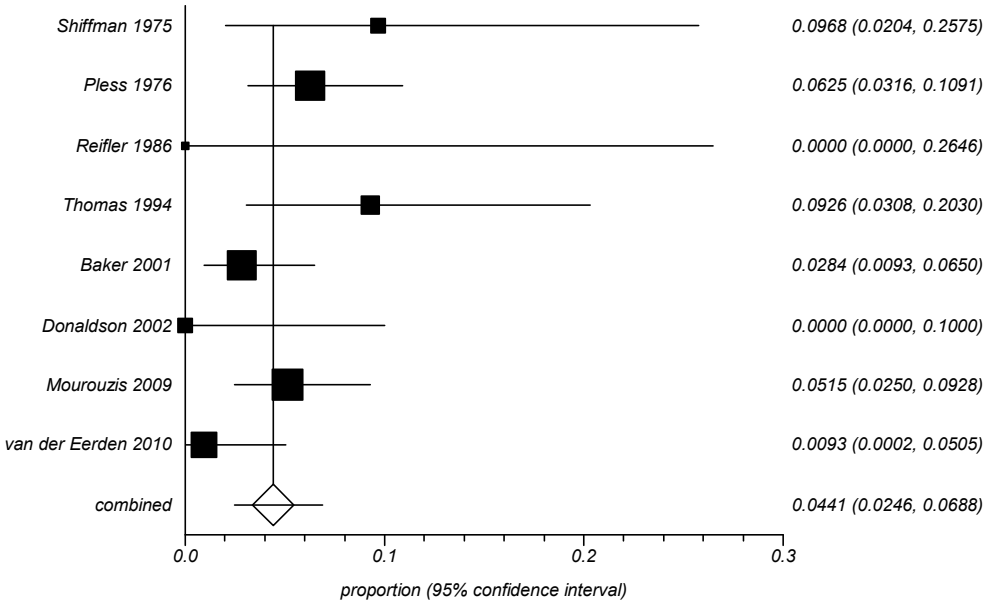


Figure 23: Surgical excision regional recurrence proportion meta-analysis [random effects]

Sensitivity analysis in which only the three papers considered at lowest risk of bias were included had no significant effect on regional recurrence (4.6% [95%CI 1.3 to 10.0, I^2=72%] (van der Eerden et al., 2010, Thomas and Matthews, 1994, Mourouzis et al., 2009).

One study (108 patients) (van der Eerden et al., 2010) had a mean duration of follow-up of less than 2 years, with 0.1% recurrence (95% CI 0 to 5.1). In four studies, (Baker et al., 2001, Donaldson et al., 2002, Reifler and Hornblass, 1986, Mourouzis et al., 2009) specified mean duration of follow-up was between 2 and 5 years with pooled average recurrence of 3.6% (95% CI 1.9 to 5.9, I^2=11%). None of the studies had mean follow-up of greater than 5 years, and in three papers, follow-up duration was either not specified or given as a broad range (Thomas and Matthews, 1994, Shiffman, 1975, Pless, 1976).

The pooled average regional recurrence in those series in which only SCCs located around the ear were treated was 7.7% (95% CI 4.8 to 11.2, I^2=0%) (Thomas and Matthews, 1994, Shiffman, 1975, Pless, 1976), which was substantially greater than the pooled average regional recurrence of 2.9% (95% CI 1.4 to 5.0, I^2=27%) for the five remaining studies which included other

head and neck locations (Reifler and Hornblass, 1986, Donaldson et al., 2002, van der Eerden et al., 2010, Baker et al., 2001, Mourouzis et al., 2009)(Figure 24 and Figure 25).

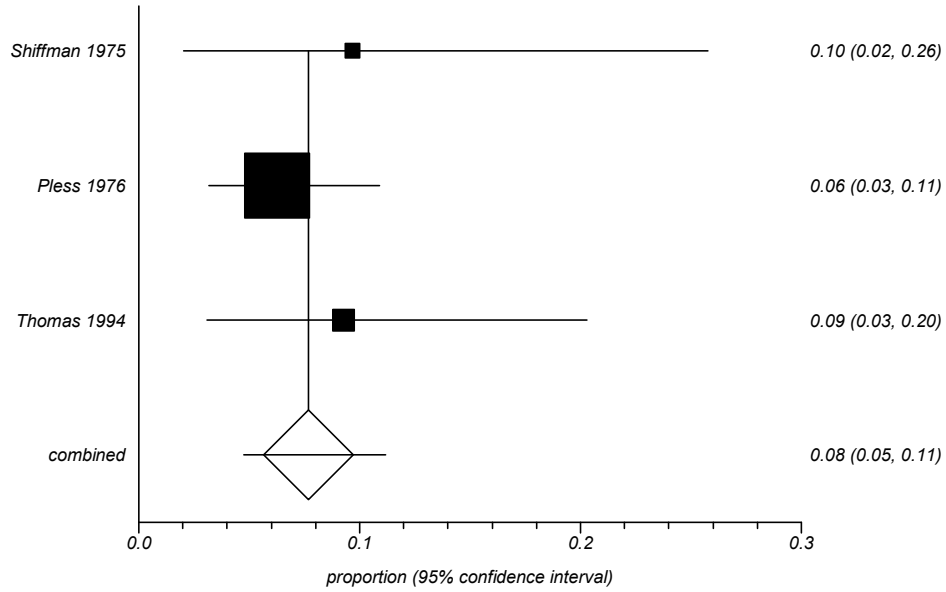


Figure 24: Surgical excision regional recurrence ear location proportion meta-analysis plot [random effects]

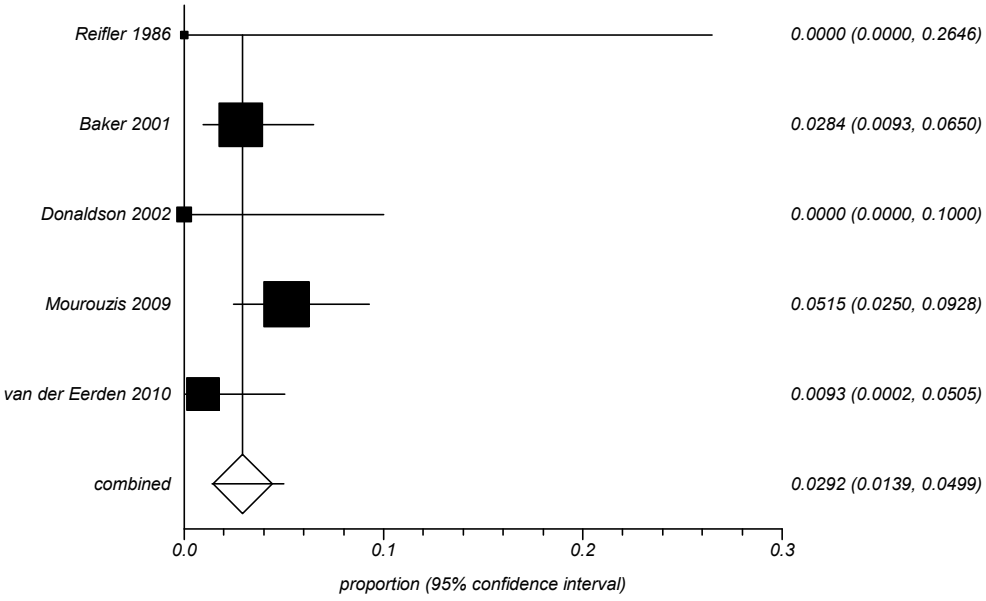


Figure 25: Surgical excision regional recurrence non-ear location proportion meta-analysis plot [random effects]

There were two studies which reported distant metastases after surgical excision. Of 211 patients with SCCs at various sites who were followed up for at least a year, only one developed distant metastasis (Knox et al., 1967). There were no distant metastases in any of 35 patients with periocular SCC during a mean follow-up period of 31.1 months (Donaldson et al., 2002).

In four articles (comprising 146 patients), recurrence was reported but not defined as being local, regional or distant. Two of these studies had mean follow-up periods greater than 5 years, with pooled average recurrence of 5.8% (95% CI 0.7 to 27.6) (Ang et al., 2004, Friedman et al., 1984). There were no reported recurrences in the study in which mean follow-up was less than 5 years (Werlinger et al., 2002). The fourth study included 13 patients with stage I or II SCC of the external ear, with a relatively high recurrence of 61.5% (95% CI 31.6 to 86.1) during follow-up which ranged from 6 months to 20 years (Yoon et al., 1992).

From analysis of eight studies (485 patients) with primary SCC, deaths attributable to disease ranged from 0% to 8.1% during follow-up, with a pooled average of 4.1% (95% CI 1.7 to 7.6, I^2=58%)(Reifler and Hornblass, 1986, Donaldson et al., 2002, Baker et al., 2001, Thomas and Matthews, 1994, Shiu et al., 1980, Friedman et al., 1984, Shiffman, 1975, Griffiths et al., 2002)(Figure 26). Three studies in which the follow-up period was specified as between 2 and 5 years (Reifler and Hornblass, 1986, Baker et al., 2001, Donaldson et al., 2002) had a significantly lower pooled average of 0.8% (95% CI 0 to 2.5, I^2=0%), than the two studies with follow-up of more than 5 years from which the pooled average percentage of patients dying from their disease was 8.6% (95% CI 4.7 to 13.6)(Friedman et al., 1984, Griffiths et al., 2002). In three papers, duration of follow-up was not specified or was given as a range only (Shiu et al., 1980, Thomas and Matthews, 1994, Shiffman, 1975) No deaths were reported in either of the two included studies in which SCCs of the eyelid were surgically excised (Reifler and Hornblass, 1986, Donaldson et al., 2002).

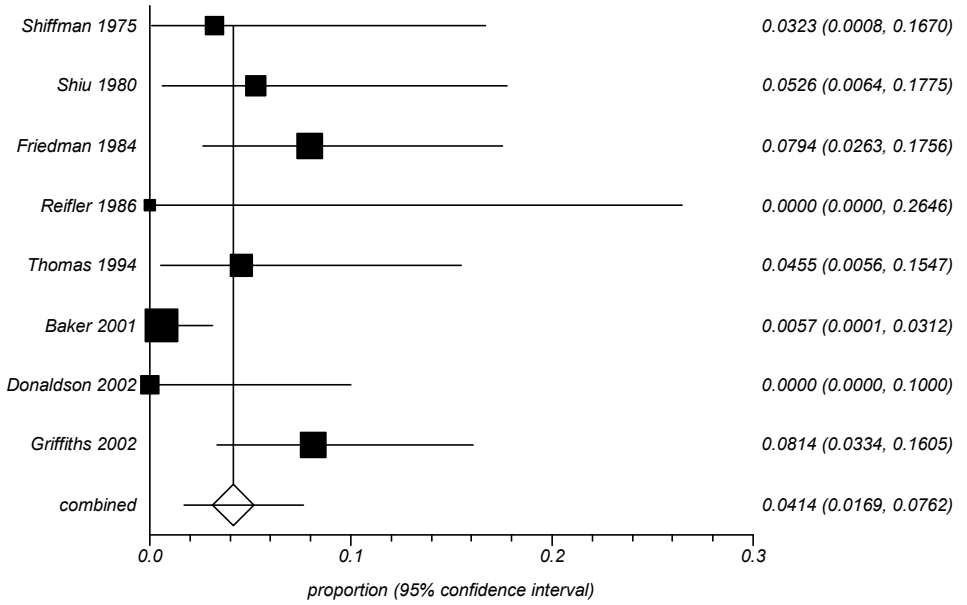


Figure 26: Surgical excision deaths attributable to disease proportion meta-analysis plot [random effects]

Incompleteness of surgical excision was reported in 11 studies (comprising 2343 excisions). Overall, the pooled average estimate of incomplete excisions was 8.8% (95% CI 5.3 to 13.0, I^2=89%) (Pua et al., 2009, Tan et al., 2007, Baker et al., 2001, Thomas and Matthews, 1994, Ang et al., 2004, Bovill et al., 2009, Nemet et al., 2006, Griffiths et al., 2002, Thomas et al., 2003, Bogdanov-Berezovsky et al., 2005)(Figure 27). Definitions of incomplete excision within the studies were not consistent, with four studies basing their definition as the presence of tumour cells at the surgical margin (Bogdanov-Berezovsky et al., 2005, Pua et al., 2009, Tan et al., 2007, Mourouzis et al., 2009), one study as the presence of residual tumour at or within 1mm of the lateral or deep margins of the excised specimen (Ang et al., 2004), one study as tumour within one microscopic high-power field (0.5mm) (Thomas et al., 2003), and a further study as the presence of tumour at or 'close to' the margin of the resected specimen (Bovill et al., 2009).

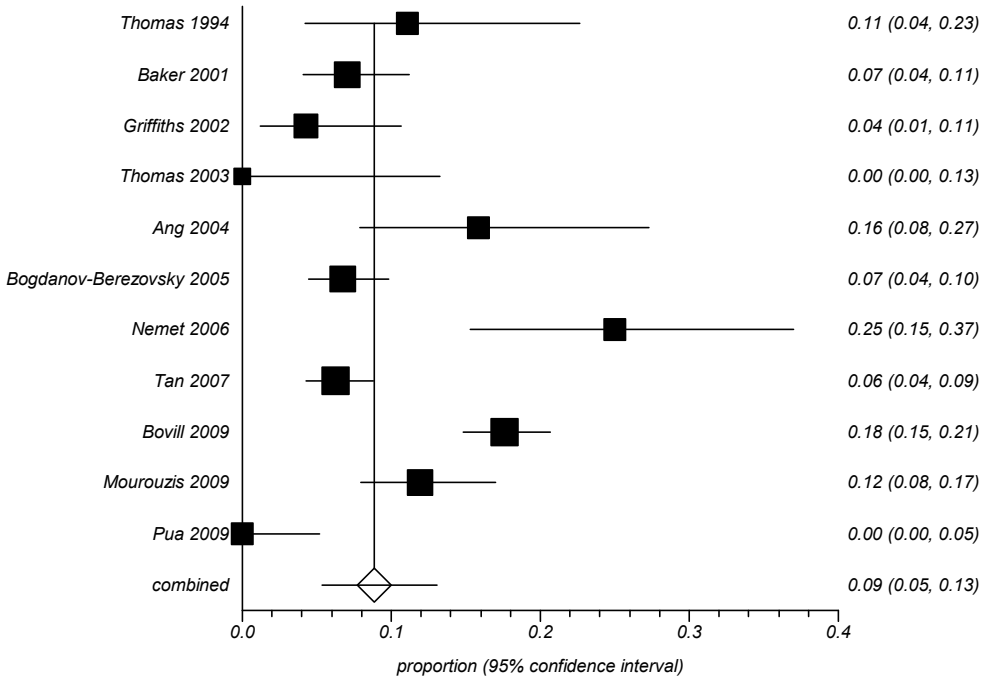


Figure 27: Surgical excision incomplete excision proportion meta-analysis [random effects]

There was variation in the excision margins employed. In one prospective study, margins of 2mm to more than 10mm were used (Tan et al., 2007), with 6.2% of tumours being incompletely excised (95% CI 4.2 to 8.8). In a further prospective series in which none of the SCCs were incompletely excised, excision margins were based on the clinical diagnosis and surgeon's preference (Thomas et al., 2003). The other studies assessing incomplete excision were retrospective reviews and in those in which the excision margin was specified, margins between 3mm to 6mm were used (Pua et al., 2009, Ang et al., 2004, Nemet et al., 2006, Mourouzis et al., 2009, Bogdanov-Berezovsky et al., 2005). The highest percentage of incompletely excised tumours were observed after excision of periorbital lesions with a 5mm margin, with 25% being incompletely excised (95% CI 15.3 to 37.0) (Nemet et al., 2006).

None of the included studies reported SCC specific quality of life, cosmetic appearance, or adverse event data.

Summary: Surgical excision

- Twelve studies, mostly retrospective case series of limited quality and with follow-up periods which varied between studies
- Local recurrence varied due to different time points when assessed, with average recurrence of 5.4% (95% CI 2.5 to 9.1,12 studies, N=1144)
- Regional recurrence average estimate 4.4% (95% CI 2.4 to 6.9, 8 studies, N=786)
- Higher rates of local and regional recurrence seen in those treated with SCC of the ear
- Unspecified recurrence average 5.8% (95% CI 0.7 to 27.6, 2 studies, N= 113)
- Death from disease average 4.1% (95% CI 1.7 to 7.6, 8 studies, N=485)
- Increased proportion of deaths attributable to disease in studies with follow-up longer than 5 years compared with follow-up between 2 and 5 years 8.6%(95% CI 4.7 to 13.6, 2 studies, N=149) v 0.8% (95% CI 0.1 to 2.5, 3 studies, N=223)
- Incomplete excision average 8.8% (95%CI 5.4 to 13.0, 11 studies, N=2343)

4.4.4. Mohs Micrographic Surgery

Sixteen studies reported outcomes after MMS. In a seminal series of papers, Mohs reported 5-year cure rates for previously untreated SCCs of 95.7% for SCC of the trunk and extremities (Mohs, 1978); 96.6% for the ear (Mohs et al., 1988); 97.8% for facial, scalp and neck SCCs (Mohs, 1978); 98.5% for eyelid SCCs (Mohs, 1986); and 98.8% for SCCs of the nose (Mohs, 1978);a pooled 5-year cure rate 97.4% for the 2133 SCCs at all sites (95% CI 96.2 to 98.3, I^2=48%).

Ten studies reported local recurrence (Anderson, 1982, Pugliano-Mauro and Goldman, 2010, van der Eerden et al., 2010, Vuyk and Lohuis, 2001, Turner et al., 2000, Silapunt et al., 2005, Malhotra et al., 2004, Brantsch et al., 2008, Leibovitch et al., 2005a, Dzubow et al., 1982) , ranging from 0% (95% CI 0 to 36.9) in one small study including eight periorbital SCCs (Anderson, 1982), up to 5.7% (95% CI1.9 to 12.9) in a study of auricular SCCs (Silapunt et al., 2005). For the ten studies (comprising 1572 participants), the pooled average local recurrence was 3.0% (95% CI 2.2 to 3.9, I^2=0%) (Figure 28).

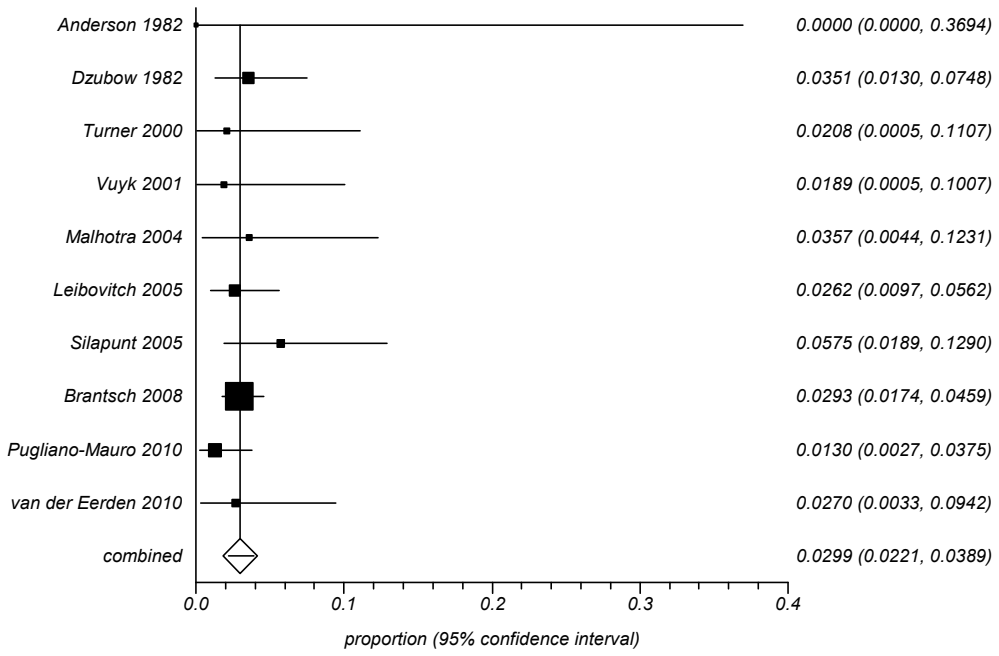


Figure 28: MMS local recurrence proportion meta-analysis plot [random effects]

Sensitivity analysis, including only the six studies meeting the pre-specified criteria, had no significant impact on local recurrence (2.7%; 95% CI 1.9 to 3.7, I^2=0%)(Turner et al., 2000, Malhotra et al., 2004, Pugliano-Mauro and Goldman, 2010, van der Eerden et al., 2010, Brantsch et al., 2008, Leibovitch et al., 2005a).

Recurrence in the one study with specified mean follow-up of less than 2 years (Dzubow et al., 1982) was 3.5% (95% CI 1.3 to 7.5), which did not differ significantly from the average recurrence of 2.8% (95% CI 2.0 to 3.9, I^2=0%) in seven studies with mean follow-up of between 2 and 5 years (Anderson, 1982, Pugliano-Mauro and Goldman, 2010, Silapunt et al., 2005, Turner et al., 2000, van der Eerden et al., 2010, Vuyk and Lohuis, 2001, Brantsch et al., 2008, Dzubow et al., 1982), and 3.1% (95% CI 1.4 to 5.4) in the two studies with mean follow-up greater than 5 years (Malhotra et al., 2004, Leibovitch et al., 2005a).

Six studies reported recurrence in the regional lymph nodes after treatment with MMS (van der Eerden et al., 2010, Pugliano-Mauro and Goldman, 2010, Turner et al., 2000, Anderson, 1982, Brantsch et al., 2008, Cherpelis et al., 2002). On pooled analysis (comprising 1162 patients) the average regional recurrence was 4.2% (95% CI 2.3 to 6.6, I^2=56%; Figure 29). There was no significant impact on regional recurrence in the sensitivity analysis, which included only four studies meeting the criteria (Turner et al., 2000, Pugliano-Mauro and Goldman, 2010, van der Eerden et al., 2010, Brantsch et al., 2008), with average recurrence of 3.2% (95% CI 1.9 to 5.0, I^2=29%).

Specified mean follow-up was between 2 and 5 years in five studies (Anderson, 1982, Pugliano-Mauro and Goldman, 2010, Turner et al., 2000, van der Eerden et al., 2010, Brantsch et al., 2008), with pooled regional recurrence of 3.4% (95% CI 1.8 to 5.3, I^2=34%). None of the studies had mean follow-up greater than 5 years.

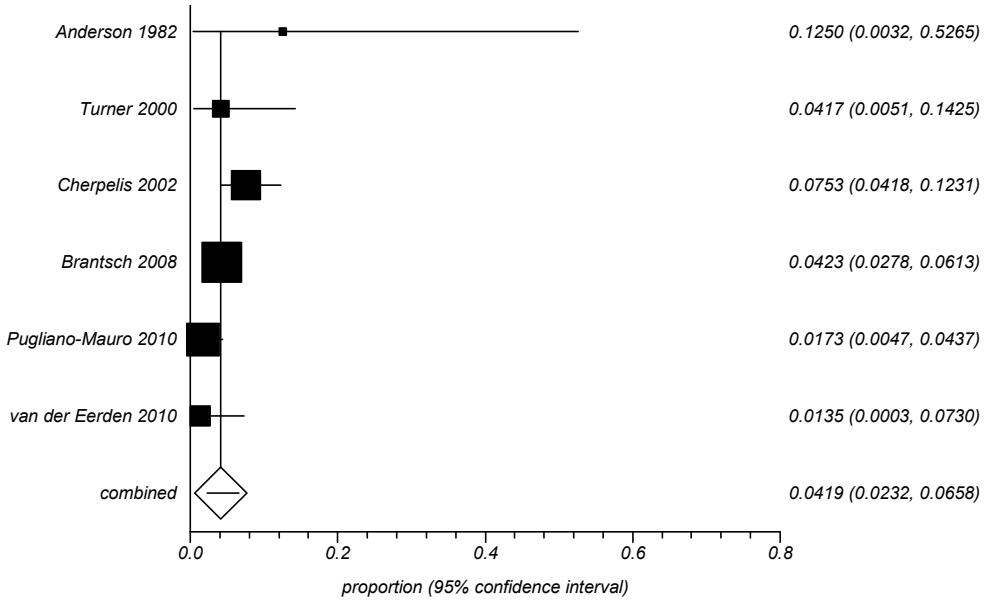


Figure 29: MMS regional recurrence proportion meta-analysis plot [random effects]

One study reported no distant metastases during at least 5 years of follow-up in 229 patients treated with MMS (Leibovitch et al., 2005a). In a case series of 87 auricular SCCs, no distant metastases were reported during a mean follow-up period of 34.6 months (Silapunt et al., 2005). One smaller series of 48 SCCs treated by MMS observed one patient with distant metastasis during a mean follow–up of 3.4 years (Turner et al., 2000), and a further series including eight patients with periocular SCC also noted one patient with metastases to the lung (Anderson, 1982), although the authors presumed that this patient had subclinical spread of tumour prior to treatment with MMS as there was no evidence of local recurrence.

Five studies (766 patients) did not define recurrence as being local, regional or distant (Tomsick and Menn, 1984, Mohs, 1976, Skaria, 2010, Thomas et al., 2007, Yoon et al., 1992) with a pooled average unspecified recurrence of 4.7% (95% CI 0.7 to 11.7, I^2=81%) (Figure 30). The highest proportion of unspecified recurrences was seen in a small series of 16 external ear SCCs during follow-up of between 6 months to 20 years, in which 31% of tumours recurred (95% CI 11.7 to 58.7)(Yoon et al., 1992).

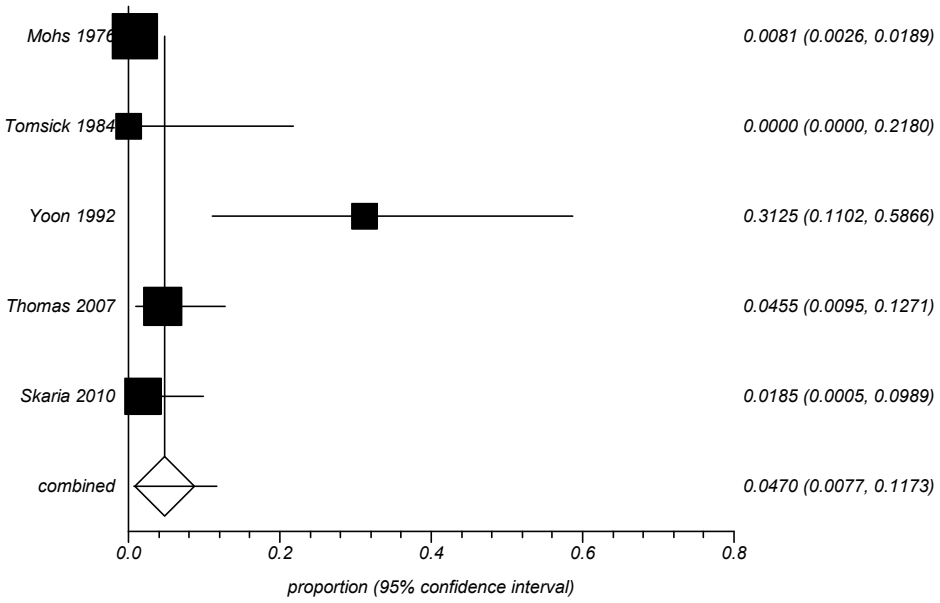


Figure 30 MMS: unspecified recurrence proportion meta-analysis plot [random effects]

Three studies (735 patients) specified mean duration of follow-up as being between 2 and 5 years (Mohs, 1976, Thomas et al., 2007, Skaria, 2010). For these studies, the average unspecified recurrence was 2.2% (95% CI 0.3 to 5.4, I^2=61%). The remaining studies (Tomsick and Menn, 1984, Yoon et al., 1992) did not specify the mean duration of follow-up.

Four studies with mean follow-up of between 2 and 5 years reported death attributable to SCC (Silapunt et al., 2005, Pugliano-Mauro and Goldman, 2010, Anderson, 1982, Brantsch et al., 2008), with an average of 1.1% (95% CI 0.2 to 2.6, I^2=49%) of the 941 eligible patients dying from disease on pooled analysis (Figure 31). One of the included studies reported a relatively high proportion of deaths compared to the other studies, which related to a small series of eight patients with periocular SCCs, one of whom developed regional metastases and lung metastases without evidence of local recurrence, indicating that the tumour had spread subclinically prior to treatment (Anderson, 1982).

None of the included studies reported separate SCC data for quality of life, cosmetic outcomes or adverse events.

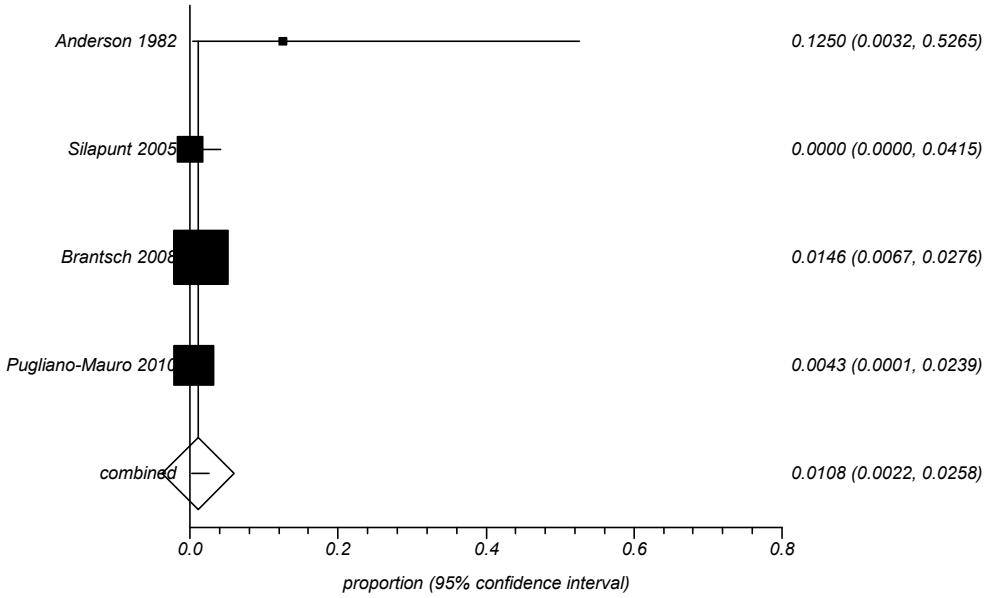


Figure 31: MMS deaths attributable to disease proportion meta-analysis plot [random effects]

Summary: Mohs Micrographic surgery

- Sixteen case series, 4 prospective and 12 retrospective.
- Local recurrence average 3.0% (95% CI 2.2 to 3.9, 10 studies, N=1572)
- Regional recurrence average 4.2% (95% CI 2.3 to 6.6, 6 studies, N=1162)
- Unspecified recurrence average 4.7% (95% CI 0.7 to 11.7, 5 studies, N=766)
- Death from disease average 1.1% (95% CI 0.2 to 2.6,4 studies, N=941)

4.4.5. External radiotherapy

There were 14, mostly retrospective, studies in which a total of 1018 primary SCCs were treated with external radiotherapy (Stoll et al., 1964, Abbatucci et al., 1989, Knox et al., 1967, Rank, 1973, Grosch and Lambert, 1979, Podd, 1992, Kwan et al., 2004, Honeycutt and Jansen, 1973, Holmes and Bomford, 1982, Barysch et al., 2012, Shiffman, 1975, Tsao et al., 2002, Matthiesen et al., 2011, Hunter et al., 1982). Seven studies (comprising 761 patients) reported local recurrence after external radiotherapy, with pooled average local recurrence of 6.4% (95% CI 3.0 to 11.0, I^2=76%)(Abbatucci et al., 1989, Rank, 1973, Stoll et al., 1964, Podd, 1992, Barysch et al., 2012, Shiffman, 1975, Tsao et al., 2002) (Figure 32). Three studies were included in the sensitivity analysis (Abbatucci et al., 1989, Barysch et al., 2012, Tsao et al., 2002), with no significant effect on local recurrence (7.3%; 95% CI 2.1 to 15.4, I^2=87%).

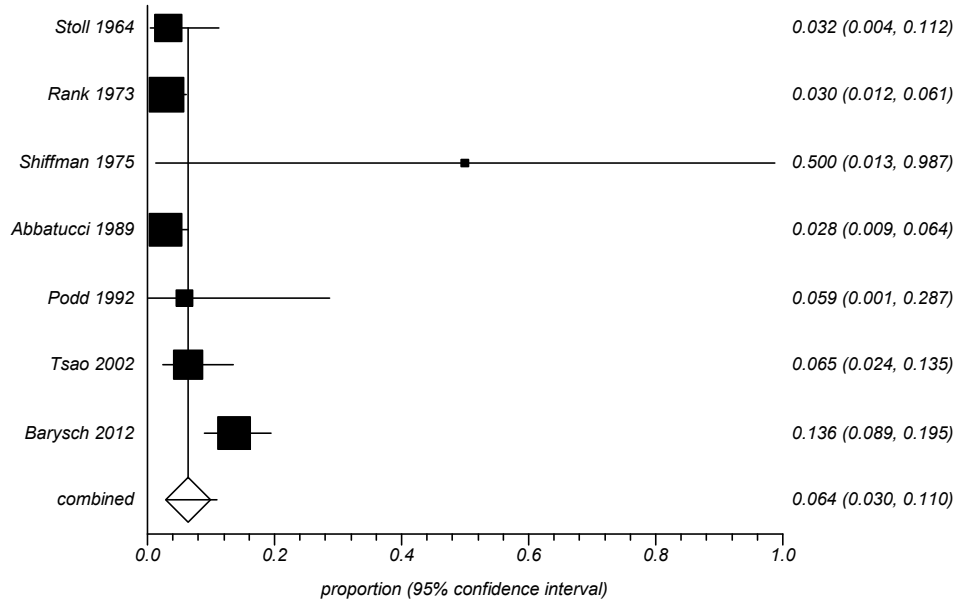


Figure 32: External radiotherapy local recurrence proportion meta-analysis plot [random effects]

From the four studies in which the mean follow-up period was between 2 and 5 years (Abbatucci et al., 1989, Barysch et al., 2012, Rank, 1973, Tsao et al., 2002) the pooled average recurrence was 6.1% (95% CI 2.2 to 11.7, I^2=85%).

None of the studies had mean follow-up greater than 5 years, and in three studies, duration of follow-up was not specified or given as a broad range (Podd, 1992, Stoll et al., 1964, Shiffman, 1975).

Location in the ear and scalp region was found to be significantly associated with relapse of tumour compared to other sites (p=0.025) in one study (Barysch et al., 2012). Age and tumour size were also significantly correlated with risk of relapse in this study (p=0.012 and p<0.0001 respectively), with a trend towards better outcome with well-differentiated tumours, although statistical significance was not reached (p=0.1). Two studies (with 155 patients in total) only assessed nasal SCCs, with a pooled average local recurrence of 5.6% (95% CI 2.6 to 9.7) (Stoll et al., 1964, Tsao et al., 2002). In a further two small studies (19 patients) which only included SCCs of the pinna, the pooled average local recurrence was 20.3% (95% CI 0.0 to 64.6)(Podd, 1992, Shiffman, 1975), although the wide confidence intervals suggest this is not significantly different from recurrence of nasal SCCs.

Regional lymph node failure was also reported in three studies (comprising 272 patients in total) (Barysch et al., 2012, Shiffman, 1975, Tsao et al., 2002), giving an average regional recurrence of 2.6% on pooled analysis (95% CI 0.04 to 8.9, I^2=70%) (Figure 33). In both larger studies (Barysch et al., 2012, Tsao et al., 2002), which included patients with SCCs of the nose and at various sites respectively, the mean duration of follow-up was between 2 and 5 years. In the third study, there were only two eligible patients with SCC of the pinna, one of whom developed metastasis (Shiffman, 1975). Excluding this study from the analysis had little impact on the outcome.

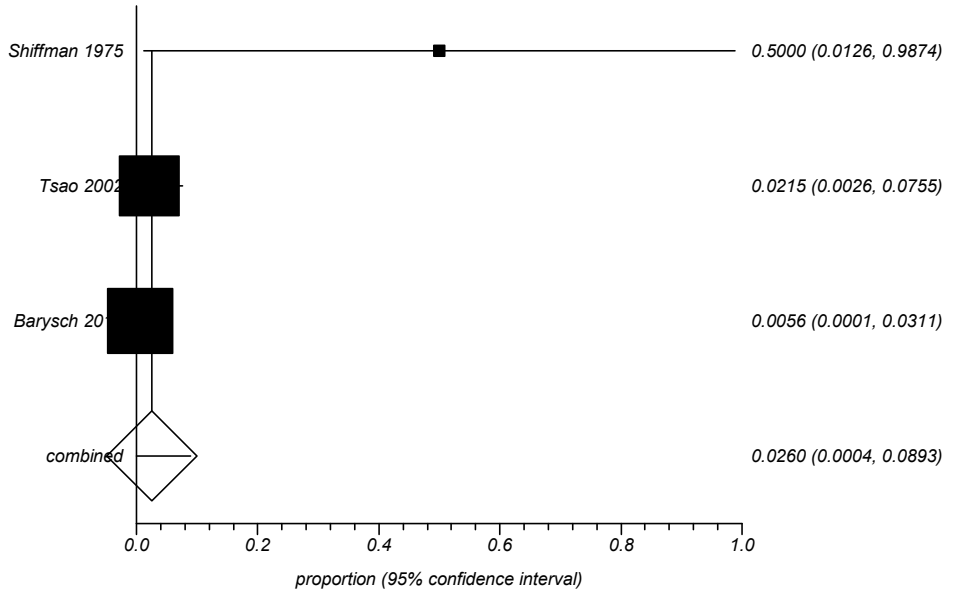


Figure 33: External radiotherapy regional recurrence proportion meta-analysis plot [random effects]

One study reported loco-regional recurrence after either local radiotherapy alone, or after local radiotherapy plus radiotherapy to first echelon lymph nodes (Kwan et al., 2004). Overall recurrence in the 37 SCCs treated with local radiotherapy alone was 30.0% (95% CI 15.9 to 47.0), ranging from 14.3% (0.3 to 57.9) for the seven tumours classified as T2, to 29.2% (95% CI 12.6 to 51.1) of the 24 T3 tumours, up to 50% (95% CI 11.8 to 88.2) for the six T4 tumours. However, with wide overlapping confidence intervals, statistical significance cannot be inferred from these differences. For the five T4 tumours which were treated with local radiotherapy plus nodal radiotherapy there was one (20%) recurrence (95% CI 0.5 to 71.6).

Recurrence was not defined as local, regional or distant in a further six studies (Holmes and Bomford, 1982, Grosch and Lambert, 1979, Honeycutt and Jansen, 1973, Knox et al., 1967, Matthiesen et al., 2011, Hunter et al., 1982). Pooled data from the 220 treated SCCs from the studies gave an average recurrence of 4.8% (95% CI 0.6 to 12.8, I^2=70%; Figure 34*).*

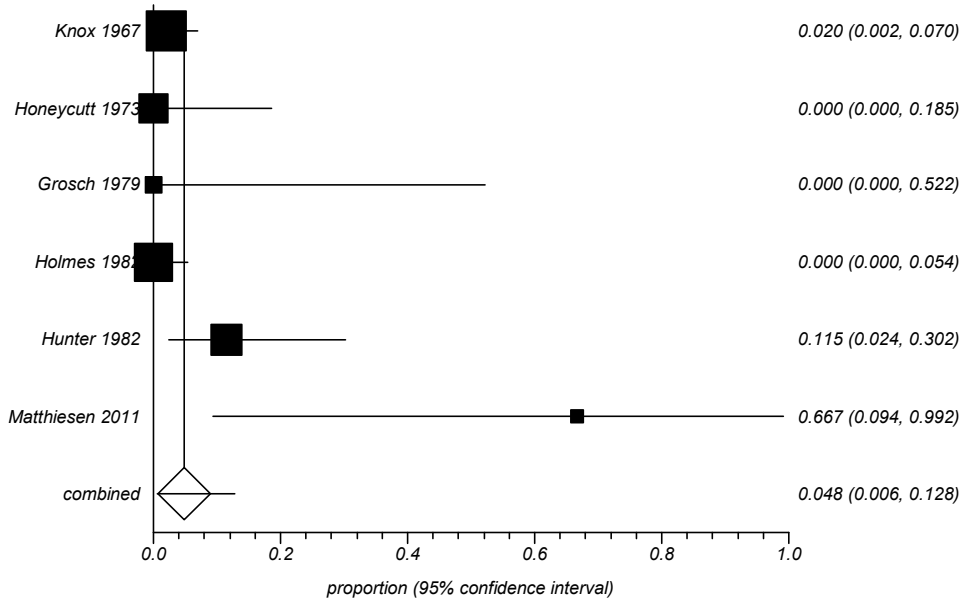


Figure 34: External radiotherapy unspecified recurrence proportion meta-analysis plot [random effects]

Two of the studies (Grosch and Lambert, 1979, Matthiesen et al., 2011) had a mean duration of follow-up of less than 2 years with pooled recurrence of 27.2% (95% CI 2.0 to 89). However, the total number of patients in the two studies was very small (5), and in one of the studies (Matthiesen et al., 2011), only T4 tumours were treated with recurrence in two out of three patients. Average recurrence in the two studies with specified mean duration of follow-up of between 2 and 5 years was 6.1% (44 patients, 95% CI 0 to 22.6)(Honeycutt and Jansen, 1973, Hunter et al., 1982). There were no studies in which the mean follow-up period was greater than 5 years, with unspecified mean follow-up duration on the remaining two studies (Knox et al., 1967, Holmes and Bomford, 1982).

There were five studies including 191 patients that reported deaths as a result of SCC (Holmes and Bomford, 1982, Shiffman, 1975, Tsao et al., 2002, Matthiesen et al., 2011, Hunter et al., 1982), with an average of 9.1% of patients dying from their disease on pooled analysis (95% CI 1.4 to 22.8, I^2=79%)(Holmes and Bomford, 1982, Hunter et al., 1982, Matthiesen et al., 2011, Shiffman, 1975, Tsao et al., 2002) (Figure 35). The greatest proportion

of deaths was observed in a study of advanced T4 tumours in which two of three patients with eligible SCCs died (66%, 95% CI 9.4 to 99.1) (Matthiesen et al., 2011), during a mean follow-up period of 14 months. For studies with mean duration of follow-up between 2 and 5 years, the average recurrence was 4.8% (119 patients, 95% CI 1.6 to 9.8) (Tsao et al., 2002, Hunter et al., 1982). None of the studies had mean duration of follow-up greater than 5 years.

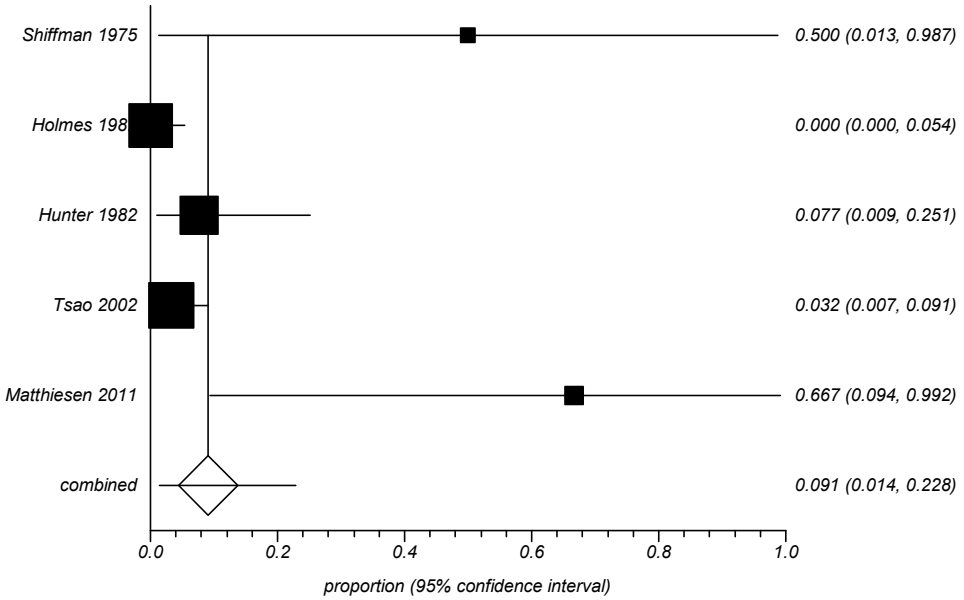


Figure 35: External radiotherapy deaths from disease proportion meta-analysis plot [random effects]

SCC specific data for cosmetic appearance and adverse events was not available from any of the included studies.

Summary: External radiotherapy

- One prospective and 13 retrospective series
- Variation between studies for radiation source and length of follow-up
- Local recurrence average 6.4% (95% CI 3.0 to 11.0, 7 studies, N=761)
- Regional recurrence average 2.6% (95% CI 0.04 to 8.9, 3 studies, N=272)
- Unspecified recurrence average 4.8% (95% CI 0.6 to 12.8, 6 studies, N=220)
- Death from disease average 9.1% (95% CI 1.4 to 22.8, 5 studies, N=191)

4.4.6. Brachytherapy

Six studies (comprising 88 SCCs) reported recurrence after brachytherapy(Allan et al., 1998, Rio et al., 2005, Lee et al., 1997, Svoboda et al., 1995, Ashby et al., 1989a, Guix et al., 2000) (Figure 36*)*, giving a pooled average local recurrence of 5.2% (95% CI 1.6 to 10.5, I^2=0%). Of these, four were prospective reports (35 SCCs) (Allan et al., 1998, Lee et al., 1997, Svoboda et al., 1995, Guix et al., 2000) and two (53 SCCs) were retrospective (Rio et al., 2005, Ashby et al., 1989a), with varying follow-up periods from an average of 9.6 months (Svoboda et al., 1995) up to a median of 55 months (Rio et al., 2005).

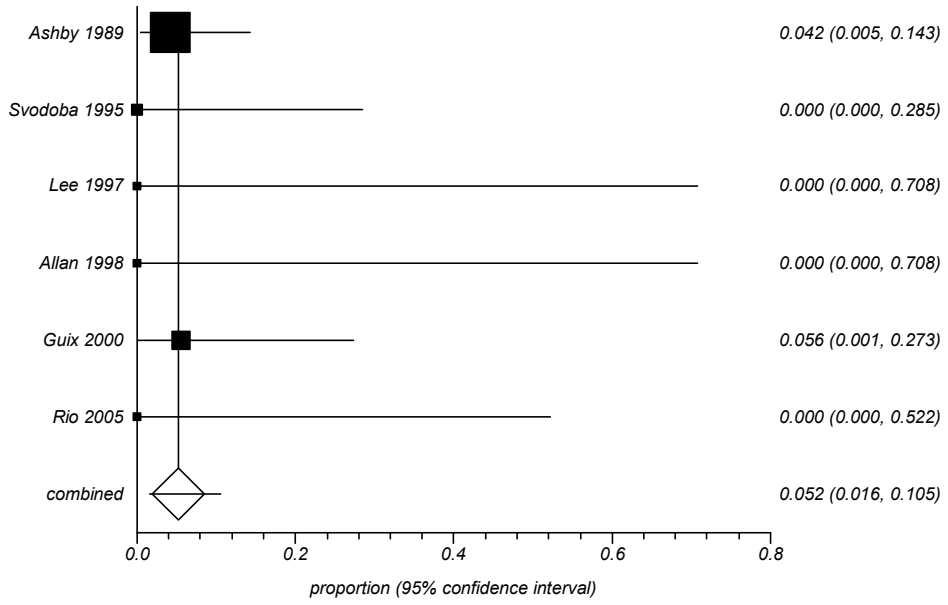


Figure 36: Brachytherapy local recurrence proportion meta-analysis plot [random effects]

Four studies had no recurrences during follow-up (Rio et al., 2005, Lee et al., 1997, Svoboda et al., 1995, Allan et al., 1998). In the largest study, a retrospective review in which 48 SCCs at various sites were treated with a superficial radon mould, there were two local recurrences of hand and scalp SCCs at 10 and 6 months respectively (Ashby et al., 1989a). The other reported SCC recurrence occurred 23 months after high dose rate brachytherapy with a ^{192}Ir surface mould and was a 4cm tumour located on the frontal area (Guix et al., 2000). No patients in this study developed regional or distant metastases after treatment.

One study reported that four of 48 (8.3%) SCCs treated with a radon mould persisted after initial treatment and required treatment by other methods to ablate the lesions (Ashby et al., 1989a). The study authors attributed their high failure rate to the inclusion of tumours with a high volume, or in which the thickness was greater than 4mm, which had been inappropriately treated by brachytherapy.

None of the included studies reported on deaths attributable to disease. Furthermore, SCC-specific data for cosmetic appearance and adverse events were not available from any of the included studies.

Summary: Brachytherapy

- Four prospective, two retrospective studies
- Variable methods of application and radiation and generally short follow-up periods
- Generally small numbers of patients
- Local recurrence average 5.2% (95% CI 1.6 to 10.5, 6 studies, N=88)
- No regional or distant metastases or deaths attributable to disease reported

4.4.7. Adjuvant radiotherapy

Nine studies were included in which adjuvant radiotherapy (ART) was used with surgery to treat previously untreated SCCs which were non-metastatic at presentation.

ART was administered for PNI in five retrospective studies (comprising 22 patients)(Osguthorpe et al., 1997, Geist et al., 2008, Cottel, 1982, DeAmbrosis and De'Ambrosis, 2010, Barrett et al., 1993). In one of these studies (DeAmbrosis and De'Ambrosis, 2010), local recurrence occurred in two of six patients with asymptomatic PNI in nerve branches of 0.4mm diameter. All excised SCCs had clear surgical margins of at least 3mm. One of these patients also had regional metastasis and the other distant metastasis after treatment. Metastasis to the skull 1 year after treatment was reported in one patient with symptomatic PNI affecting the supraorbital nerve in a further series (Cottel, 1982). In the other three studies, two of which included patients with asymptomatic PNI in unnamed nerves (Barrett et al., 1993, Geist

et al., 2008) and one in which there was involvement of named cranial nerves (Osguthorpe et al., 1997), there were no reports of recurrence following treatment during follow-up ranging from 10.4 months to 104.8 months.

Four studies (47 patients) reported outcomes after ART for SCCs other than those with PNI. These included patients with pinna SCCs , trunk and extremity SCCs (Lifeso et al., 1990, Shiffman, 1975, Khan et al., 1999, Veness et al., 1999), and those with aggressive SCCs post cardiothoracic transplant (Veness et al., 1999). The basis upon which patients were selected to receive ART as opposed to surgical monotherapy was not clearly identified in any of the studies. Three of the included studies were retrospective (Veness et al., 1999, Lifeso et al., 1990, Shiffman, 1975). The fourth was a prospective assessment of ART to draining lymph nodes in a group of patients with trunk and extremity SCCs (50% of which developed in an area of erythema-ab-igne)(Khan et al., 1999). ART was administered to the draining regional lymph nodes in both included studies of trunk and extremity SCC (Lifeso et al., 1990, Khan et al., 1999). The irradiation field was not specified in the other studies (Veness et al., 1999, Shiffman, 1975). Three of the four studies reported recurrence after treatment during follow-up ranging from less than 1 year to more than 3 years. Three patients of 26 (12%) developed local recurrence 6–12 months after treatment in the included prospective study, with regional recurrence in one patient. No distant metastases were reported during follow-up of up to 12 months (Khan et al., 1999). Local recurrence was also reported in two of six patients who developed SCC after cardiothoracic transplantation, one of whom also developed regional recurrence. A further patient in this series also had a ‘systemic’ relapse despite local control of their SCC (Veness et al., 1999).

One study reported two deaths (of four eligible patients) attributable to SCC at 6 and 11 months post treatment for PNI involving named cranial nerves. Both patients had intracranial disease extending through a peripheral foramen but had refused an intracranial operation (Osguthorpe et al., 1997). No deaths attributable to SCC after ART treatment for PNI were reported in

any of the remaining three studies (16 patients) (DeAmbrosis and De'Ambrosis, 2010, Barrett et al., 1993, Geist et al., 2008).

Three studies (comprising 21 patients) addressing ART of other SCCs had data on patient deaths, with one reporting the death of three patients out of six who had post cardiothoracic transplant SCCs between 8 months and 54 months after diagnosis (Veness et al., 1999). No deaths were reported in the other studies (Lifeso et al., 1990, Shiffman, 1975), which included patients with trunk and extremity SCCs, and those with SCC of the pinna (Pooled data are presented in Table 8).

Table 8: Outcomes after adjuvant radiotherapy

	Proportion of patients (95% CI), I^2, Number of patients			
	Local recurrence	**Regional recurrence**	**Distant metastases**	**Patient died from disease**
Adjuvant radiotherapy for perineural invasion (Cottel, 1982, Geist et al., 2008, Barrett et al., 1993, DeAmbrosis and De'Ambrosis, 2010, Osguthorpe et al., 1997)	18.2% (3.8% to 39.8%), I^2= 37%, n=22	8.3% (1.1% to 21.4%), I^2= 0%, n=22	11.5 (2.4% to 26.1%), I^2= 1%, n=22	11.1% (0.4% to 33.1%), I^2=45%, n=20
Adjuvant radiotherapy for other types of SCC (Khan et al., 1999, Lifeso and Bull, 1985, Shiffman, 1975, Veness et al., 1999)	11.1% (2.4% to 25.0%), I2= 35%, n=47	8.5% (2.5% to 17.6%), I2= 0%, n=47	3.2% (0.1% to 10.4%), I2= 9%, n=47	13.9% (0.05% to 50.2%), I2= 74%, n=21

In one study, initial failure of wide local excision and ART to control disease locally was reported in one patient (of 6) (Veness et al., 1999), who died 15 months after treatment.

Mild erythema, dry and moist desquamation and alopecia of hair-bearing areas in the irradiated field after ART were the most commonly reported adverse events in included studies (Barrett et al., 1993, Khan et al., 1999, Cottel, 1982). Single adverse events recorded were wound infection and serous otitis media (Barrett et al., 1993), self-limiting mucositis, radiation dermatitis and residual mild xerostomia (Geist et al., 2008) , and reactive lymphoedema of the leg (Khan et al., 1999).

Summary: ART

ART for PNI:

Five small retrospective studies

- Local recurrence average 18.2% (95% CI 3.8 to 39.8, 5 studies, N= 22)
- Regional recurrence average 8.3% (95% CI 1.1 to 21.4, 5 studies, N=22)
- Distant metastasis average 11.5% (95% CI 2.4 to 26.1, 5 studies, N=22)
- Death from disease average 11.1% (95% CI 0.4 to 33.1, 4 studies, N=20)

ART for other SCCs:

One prospective, three retrospective small studies

- Local recurrence average 11.1% (95% CI 2.4 to 25.0, 4 studies, N=47)
- Regional recurrence average 8.5% (95% CI 2.5 to 17.6, 4 studies, N=47)
- Distant metastasis average 3.2% (95% CI 0.1 to 10.4, 4 studies, N=47)
- Death from disease average 13.9% (95% CI 0.04 to 50.2, 3 studies, N=21)

4.4.8. Curettage and electrodesiccation

Only one small retrospective study of 15 patients with SCC of the pinna described local and regional recurrence separately after treatment by curettage and electrodesiccation (Shiffman, 1975). Of the 15 patients included, three had local recurrence (20%), of whom one (7%) developed regional disease and two died as a result of their disease.

Seven studies (comprising 1131 patients) which included SCCs from various sites reported on recurrence after curettage and electrodesiccation, but did not specify the nature of the recurrence (Knox et al., 1967, Honeycutt and Jansen, 1973, Reschly and Shenefelt, 2010, Tromovitch, 1965, Whiting, 1978, Williamson and Jackson, 1964, Werlinger et al., 2002). On pooled analysis, average recurrence was 1.7% (95% CI 0.6 to 3.4, I^2=59%) (Figure 37). A sensitivity analysis was not performed as none of the studies met the criteria for this (outlined in section 4.3.8).

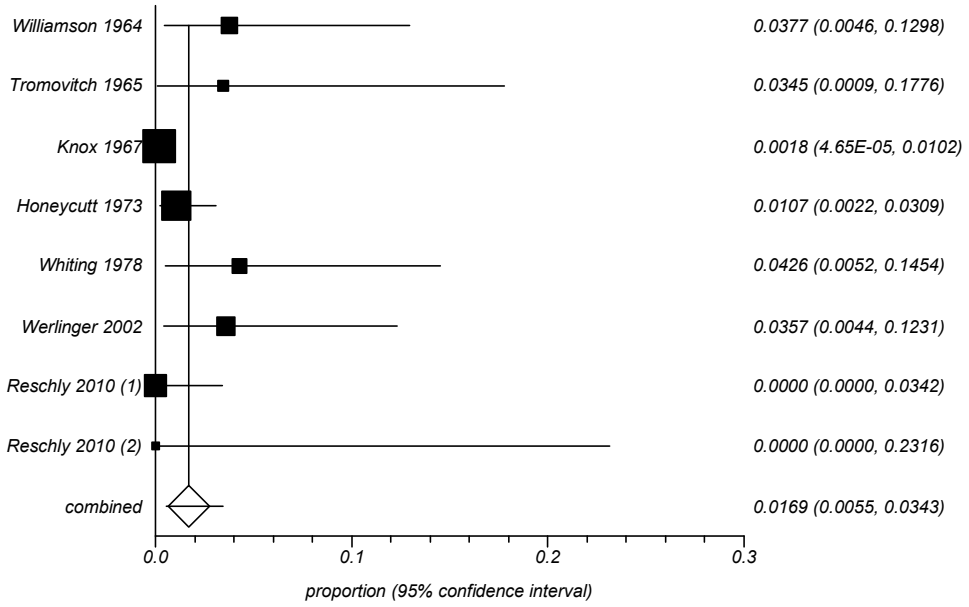


Figure 37: Curettage and electrodesiccation unspecified recurrence proportion meta-analysis plot [random effects] (1) triple cycles of CED (2) double cycles of CED

For the two studies (Werlinger et al., 2002, Williamson and Jackson, 1964) with specified mean follow-up periods between 2 and 5 years, the pooled recurrence was 4.5% (109 patients, 95% CI 1.4 to 9.0). Just one study (Tromovitch, 1965) had a mean follow-up of more than 5 years, with recurrence in 1 of 29 patients (3.4%; 95% CI 0 to 17.8). The remaining studies did not specify mean duration of follow-up.

Most of the treated SCCs in these series were small, with a total of 91% having a diameter less than 2cm in the studies in which data about diameter were provided (Knox et al., 1967, Honeycutt and Jansen, 1973, Reschly and Shenefelt, 2010, Williamson and Jackson, 1964). Increased lesion size as a significant prognostic feature was observed in one study; recurrence in the 17 SCCs larger than 2cm was 11.8% (95% CI 1.4 to 36.4) compared with 0.4% (95% CI 0.0 to 2.1) in the 264 SCCs smaller than 2cm (Honeycutt and Jansen, 1973). One study separated results according to the number of treatment cycles used with no recurrences after either two or three cycles (Reschly and Shenefelt, 2010). Two studies specified the number of cycles of electrodesiccation as either double (Tromovitch, 1965), or triple (Whiting, 1978) but this information was not reported for the remaining studies.

Cosmetic outcome was reported in just one of the included studies (41 patients) (Whiting, 1978), and rated as 'good' in 29% of SCCs, 'satisfactory' in 54% or 'poor' in 17%, although no definition of each of these terms was provided and it was unclear how soon after treatment the assessment of cosmesis was made.

None of the included studies reported adverse event data.

Summary: curettage and electrodesiccation

- Eight retrospective series of variable follow-up periods
- Treated SCCs mostly <2cm diameter
- Unspecified recurrence average 1.7% (95% CI 0.5 to 3.4, 7 studies, N=1131)
- 20% recurrence after curettage and electrodesiccation of pinna SCC (1 study, N=20)
- Lesion size >2cm significantly greater average recurrence than those <2cm: 11.8% (95% CI 1.4 to 36.4, 17 SCCs) versus 0.4% (95% CI 0.0.0 to 2.1, 264 SCCs, 1 study)

4.4.9. Cryotherapy

There were eight studies (comprising 273 patients) that described recurrence after cryotherapy (Kuflik, 2004, Fraunfelder et al., 1980, Kuflik, 1986, Fontana and Muti, 1975, Nordin and Stenquist, 2002, Peikert, 2011, Lindemalm-Lundstam and Dalenback, 2009, Holt, 1988). Only one of these reported a case of recurrence after cryotherapy (Holt, 1988), from a study population of 34 patients with SCCs at any site who were treated with a double freeze-thaw cycle using liquid nitrogen. Data from the 273 patients in the eight studies gave a pooled average recurrence of 0.8% (95% CI 0.1 to 2.2, I^2=0% (See Figure 38). Sensitivity analysis was not conducted as only one study met the pre-specified criteria outlined in section 4.3.8 (Lindemalm-Lundstam and Dalenback, 2009), with no reported recurrences (53 patients; 95% CI 0 to 6.7).

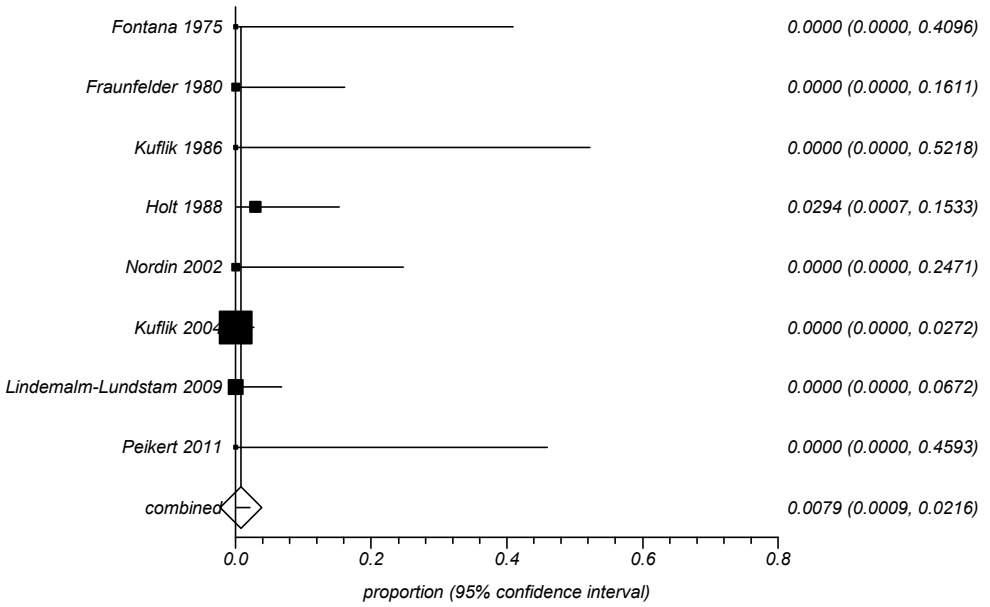


Figure 38: Cryotherapy unspecified recurrence proportion meta-analysis plot [random effects]

In five studies (Fontana and Muti, 1975, Fraunfelder et al., 1980, Kuflik, 2004, Lindemalm-Lundstam and Dalenback, 2009, Peikert, 2011) the mean duration of follow-up was between 2 and 5 years, with pooled average recurrence of 0.4% (221 patients; 95% CI 0 to 1.7, I^2=0%). None had mean follow-up of greater than 5 years, and for three studies (Holt, 1988, Kuflik, 1986, Nordin and Stenquist, 2002) follow-up was given as a range only.

An overall cure rate of 97% was reported after either a single or double freeze-thaw cycle with liquid nitrogen in a retrospective series of 563 SCCs at any site which were treated over a 23-year period (Graham and Clark, 1990). The authors did not define 'cure', so this rate may include lesions which failed to respond to the initial treatment in addition to those which recurred. The duration of follow-up was not specified.

Failure to respond to initial treatment was reported in one patient of 34 (3%) in one prospective series (Holt, 1988). A double freeze-thaw cycle was used to treat the original SCC, a 5mm lesion on the scalp, which showed little clinical response despite a second course of cryotherapy 2 months after the initial treatment.

None of the studies in which cosmetic appearance and adverse events were reported separated results obtained for SCCs and BCCs treated by cryotherapy, but presented results for NMSCs as a whole.

Summary: cryotherapy

- Six prospective, three retrospective series with variable follow-up periods
- Mostly <2cm diameter, low-risk lesions
- Recurrence average 0.8% (95% CI 0.1 to 2.2, 8 studies, N=273)

4.4.10. Photodynamic therapy

There were 14 small prospective studies (comprising 297 patients) which evaluated the response of SCCs to PDT (Lui et al., 1995, Baptista et al., 2006, Calzavara-Pinton, 1995, Fink-Puches et al., 1998, Ziolkowski et al., 2004, Calzavara-Pinton et al., 2008, Haddad et al., 2004, Fritsch et al., 1998, Harth et al., 1998, Pennington et al., 1988, Wolf et al., 1993, Feyh et al., 1990, Kubler et al., 1999, Kennedy et al., 1990). Three studies separated SCCs according to level or depth of invasion (Calzavara-Pinton, 1995, Calzavara-Pinton et al., 2008, Kennedy et al., 1990), and one was a non-randomised two- arm comparison of topical PDT either with or without a 5% glycolic acid penetration enhancer (Ziolkowski et al., 2004). On pooled analysis, an average of 72.0% of treated lesions appeared to respond completely to treatment (95% CI 61.5 to 81.4, I^2=71%) (Figure 39). Five studies specified that histological assessment of at least some of the treated areas was done to confirm apparent clinical response (Calzavara-Pinton, 1995, Kubler et al., 1999, Lui et al., 1995, Pennington et al., 1988, Feyh et al., 1990).

In eight of the included studies, SCCs that had apparently completely responded to PDT initially were observed for recurrence (Baptista et al., 2006,

Calzavara-Pinton, 1995, Calzavara-Pinton et al., 2008, Fink-Puches et al., 1998, Pennington et al., 1988, Wolf et al., 1993, Feyh et al., 1990, Kubler et al., 1999). Pooled recurrence data from these studies (119 SCCs) gave an odds of recurrence of 26.4% (95% CI 12.3 to 43.7, I^2=72%) (Figure 40). Mean duration of follow-up ranged from 6 months (at which time the trial was abandoned due to recurrence in more than 50% of lesions) (Pennington et al., 1988), to 38 months (Baptista et al., 2006).

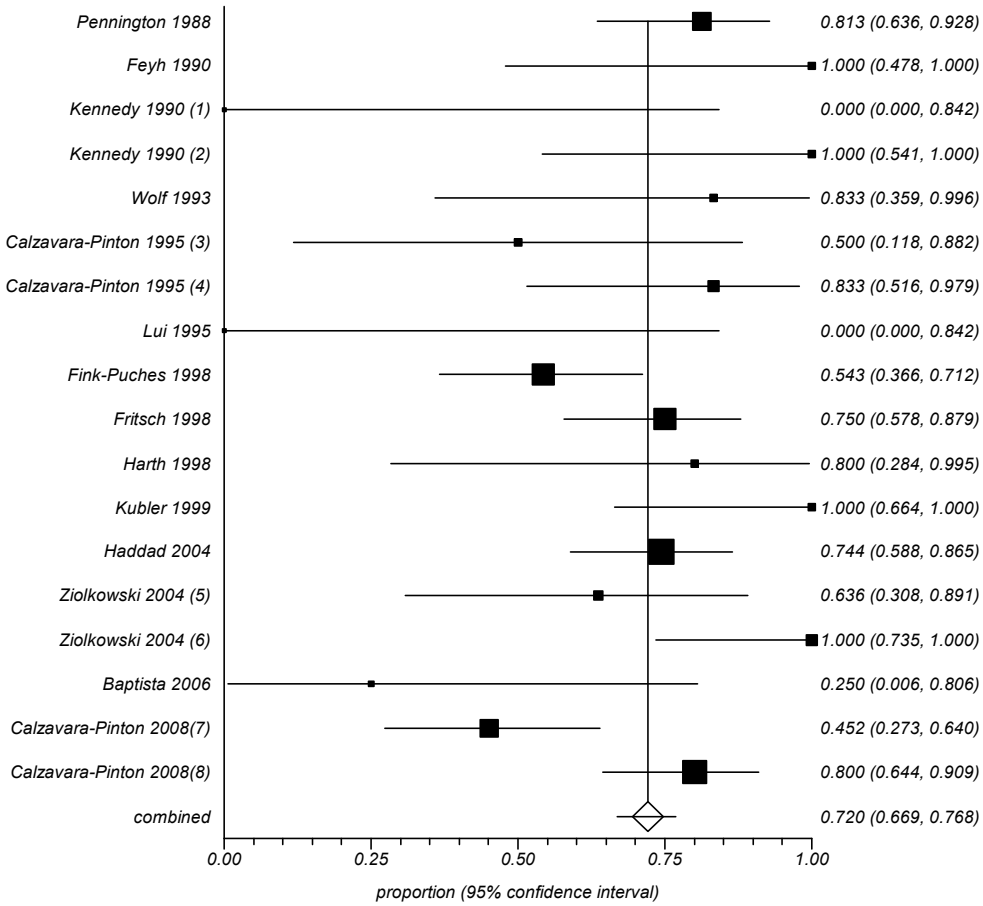


Figure 39: PDT apparent complete response proportion meta-analysis plot [random effects]

(1) 'elevated' (2) 'early invasive' (3) 'nodular' (4) 'superficial' (5) no glycolic acid (6) plus glycolic acid (7) 'invasive' (8) 'microinvasive'

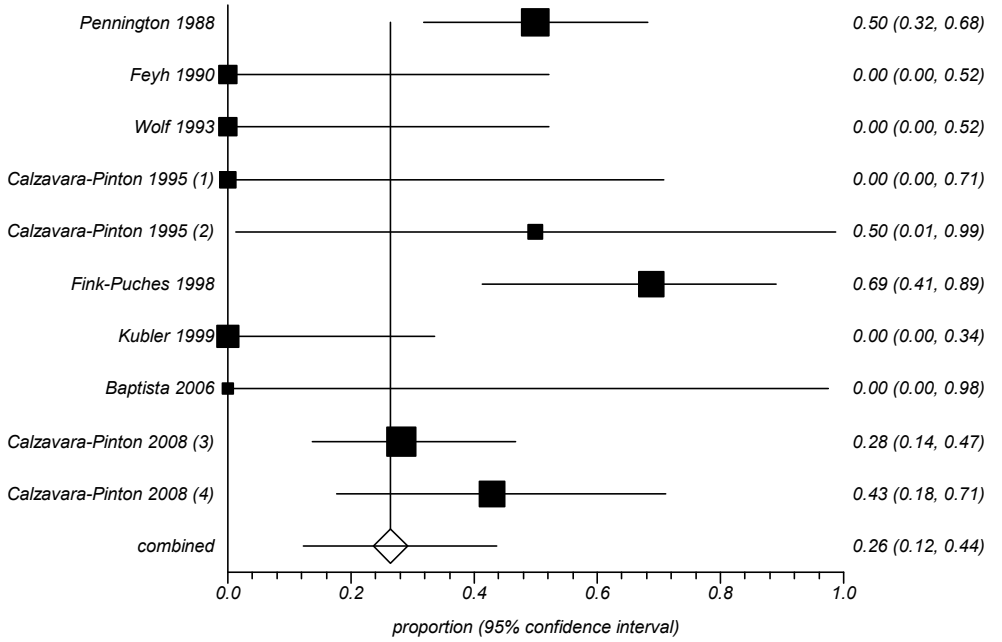


Figure 40: PDT recurrence after apparent complete response proportion meta-analysis plot [random effects] (1) 'superficial' (2) 'nodular' (3) 'microinvasive' (4) 'invasive'

One study evaluated cosmetic appearance on a scale of 1 to 4 (excellent to poor) at two time points (3 months and 24 months) after treatment (Calzavara-Pinton et al., 2008), with high agreement between patient and investigator scores for both. At 3 months, 4% of 46 treated microinvasive (Clark level II) and invasive (Clark level III/IV) SCCs were assessed as having 'excellent' cosmetic appearance, with 48% 'good', 44% 'fair' and 4% 'poor'. By 24 months, of 31 assessable treated lesions, 6% were rated as being of 'excellent' cosmetic appearance, 36% 'good', 48% 'fair' and 10% 'poor'. Tumour thickness, depth of dermal penetration and the degree of cell atypia were found by the authors to be univariate predictors of outcome (Kruskal-Wallis test $p<0.01$). One smaller study also evaluated cosmetic appearance on a scale of 1 (very good) to 4 (poor), with five (55.6%, 9 patients) treated lesions being assessed as having very good appearance, 3 (33%) as good, and 1 (11%) as fair (Kubler et al., 1999). None were deemed have poor appearance in this study. Two further studies described 'very satisfactory cosmetic results' (Ziolkowski et al., 2004), or 'very good' with no scar

formation and only transient residual hypo- or hyperpigmentation (Baptista et al., 2006).

None of the studies in which adverse events were reported separated results obtained for SCCs and BCCs treated by PDT, but presented results for NMSCs as a whole.

Summary: PDT

- Fourteen small prospective case series
- Histological confirmation of apparent initial clinical response sought in 5 of 14 studies
- Follow-up for recurrence in eight of 14 studies
- Apparent initial complete response average 72.0% (95% CI 61.5 to 81.4, 14 studies, N=297)
- Recurrence after apparent initial complete response average 26.4% (95% CI 12.3 to 43.7, 8 studies, N=119)

4.4.11. Treatments with less robust data

Laser therapy

One retrospective study examined the treatment of 86 facial SCCs (excluding eyelid carcinomas) with neodymium laser irradiation at a total dose ranging from 118 to 3520J (Moskalik et al., 2010). Patients were followed for a mean follow-up period of 8.2 years (range 5-11 years). Of a total of 3275 patients (all NMSCs) treated by neodymium laser during the study inclusion period, 438 (14%) were not followed up during the first 5 years. Overall, there were four recurrences in the remaining 86 SCC patients (4.6%). Of the 48 tumours smaller than 1cm in diameter, one recurred (2.1%, 95% CI 0.05 to 11.1), compared with 6.4% of the 31 tumours between 1 and 2 centimetres (95% CI 0.8 to 21.4), and 14.2% (95% CI 0.4 to 57.9) for the seven SCCs greater than 2cm in diameter, but with wide and overlapping confidence intervals these differences were not statistically significant.

Death from disease was not reported in this study.

One year post treatment, 65% of treated areas was assessed as having 'good' cosmetic appearance (lesion not visible) and 35% as 'acceptable' (slightly visible scarring, redness or depigmentation) by a clinician. By the third year of follow-up, 74% of areas were graded as having good appearance, and the remainder were acceptable.

Most of the observed effects in this study occurred in the first few days post-irradiation, most commonly reactive hyperaemia, oedema and slight soreness which were mild in severity and transient. No systemic adverse events were noted.

Topical Imiquimod

There were nine papers reporting the use of topical Imiquimod to treat SCCs eligible for this review. There was one prospective case series which included three patients with four SCCs (Peris et al., 2006), one retrospective case series in which there was one eligible patient with SCC (Ross et al., 2010), and the remainder were case reports of one or two patients (Eklind et al., 2003, Florez et al., 2004, Konstantopoulou et al., 2006, Martin-Garcia, 2005, Nouri et al., 2003, Oster-Schmidt and Dirschka, 2005, Oster-Schmidt, 2004).

Outcomes after treatment for these studies are summarised in Table 9.

Table 9: Outcomes after imiquimod

Study	Type of study (N=eligible patients)	Dose	Initial response	Follow-up	Recurrence	Adverse events	Cosmesis
Peris 2006	Open-label trial (3 patients/4 SCCs (temple, inner canthus, leg,forehead), all unsuitable surgical candidates)	Od/5x per wk/ 8-12 wks	4/4 complete clinical regression. No histologically evidence tumour on post-treatment biopsies.	Mean 25 months (24-27)	None	Erythema (3/3); erosion (2/3); pruritus (3/3); burning (1/3); hypopigmentation (1/3); ulceration (1/3). No systemic AEs.	-
Ross 2010	Retrospective case series (1 SCC of upper eyelid)	5x/week initially, decreased to 2x/wk due to irritation and chemical conjunctivitis	Complete clinical regression at 3 months (not confirmed histologically)	6 months	None in 6 months	Skin irritation and chemical conjunctivitis resolved when frequency of application decreased	-
Eklind 2003	Case reports (2 renal transplant patients – temple and sternum)	Self-applied 3x per wk/12 weeks	Pt 1. No evidence of SCC on 6 month biopsy Pt 2. 'Free of cancer' at 8 months	6 and 8 months	None at 6/8 months	Pt 1. Some scaling and scar at initial site at 16 weeks. Pt 2. Encrusted and inflammatory erythema 5 wks post treatment. Erythema at week 12 gradually subsiding	-

Florez 2004	Case report (SCC of leg, surgery refused)	Under occlusion every other day for 8 hours/8 weeks	No histological evidence of SCC in excised residual papule at 2 months	12 months	None	Local erythema, superficial erosive changes, discomfort. No systemic AEs.	-
Konstantopoulou 2006	Case report (1 patient/3 SCCs foot and lower leg, surgery refused, radiotherapy considered poor option)	3x per week for 8-12 hours initially then increased to 5x per week/19 weeks or no clinical evidence of residual tumour at sites showing response	Complete clinical response in 2/3 SCCs at 2 weeks with no histological evidence of invasive SCC on biopsy. One SCC failed to respond (excised)	16 months	No recurrence in 2 SCC showing complete response initially	-	-
Martin-Garcia 2005	Case report (nasal SCC, surgery refused)	Daily/2 weeks then 5x/week. Total duration 12 weeks	Complete clinical disappearance confirmed histologically 2 weeks post treatment	1 year	No local or regional recurrence	-	-
Nouri 2003	Case report (invasive superficial SCC of nasal tip, other treatments refused)	Self-applied od/6 weeks total (2 week break due to irritation)	No visible or histological SCC 1 month post treatment	4 weeks	-	Irritation and crusting midway through treatment necessitating treatment break. No visible erythema post treatment.	'Cosmetically pleasing' - no fibrosis, scarring, discolouration, residual erythema
Oster-Schmidt 2004	Case reports (2 patients with ear	Od/5x per week for 2 weeks	Histological clearance on 3	21 months and 8	No clinical evidence of	No AEs reported	'Remarkable improved cosmetic

	lobe and upper leg SCCs unsuitable for surgery)		months post treatment biopsy for both SCCs	months	recurrence at 21 months or 8 months (patient died of unrelated cause)		result'
Oster-Schmidt 2005	Case report (1 patient, SCC of back of hand, other treatments refused)	o.d. for 4 weeks initially, repeated at 6 months	Histological clearance 4 weeks after initial course	4 years	No recurrence	Oedema and mild burning. No systemic AEs.	'Excellent'

Post-treatment complete response was observed in all patients in eight of the studies (comprising 12 patients)(Peris et al., 2006, Ross et al., 2010, Eklind et al., 2003, Florez et al., 2004, Martin-Garcia, 2005, Nouri et al., 2003, Oster-Schmidt, 2004, Oster-Schmidt and Dirschka, 2005) with histological confirmation of clearance in all but one study (Ross et al., 2010). One case report of topical Imiquimod use observed no response in one of three foot and lower leg SCCs in the same patient(Konstantopoulou et al., 2006). All the studies apart from one (Nouri et al., 2003) followed patients for recurrence for varying periods ranging from 6 months to 4 years, with no reported recurrences. None of the studies reported on deaths attributable to disease.

Skin irritation was commonly reported (Peris et al., 2006, Ross et al., 2010, Eklind et al., 2003, Florez et al., 2004, Nouri et al., 2003, Oster-Schmidt and Dirschka, 2005), with chemical conjunctivitis reported in one patient with periocular SCC (Ross et al., 2010) No systemic adverse events were reported.

5-Fluorouracil (5-FU)

There were four studies in which single agent 5-fluorouracil was used to treat eligible SCCs, two of which related to intralesional treatment (Kraus et al., 1998b, Morse et al., 2003) and two to topical administration of 5-FU (Hamouda et al., 2001, Litwin et al., 1972) (Table 10).

Table 10: Studies and outcomes with 5-fluorouracil

Study	Type of study (N=eligible patients)	Dose	Initial response	Follow-up	Recurrence	Adverse events	Cosmesis
Intralesional 5-FU							
Kraus 1998	Prospective multi-centre open label pilot (23 evaluable patients with SCCs confined to upper half of reticular dermis)	Intratumoral FU/epinephrine at 1ml (30mg)/lesion/week at weekly intervals for up to 6 treatments. Mean cumulative dose 3.7ml (0.6-6ml)	22/23 histologically confirmed clearance	16 weeks (treated area)completely excised	-	19/23 (82.6%) superficial erosions, 9/23 (39.1%) necrosis, clearing several weeks after last treatment. Localised temporary alopecia around treated scalp lesions No clinically sig systemic reactions or AEs	Clinician assessed – 91% 'good' to 'excellent'. Patient assessed – 100% 'good' to 'excellent'
Morse 2003	Case report, SCC nasolabial fold	Intralesional 5-FU. 0.8-2.4ml once per week for 8 weeks. Total dose 12.8ml	No residual SCC after 8th injection	5 months	None	-	-
Topical 5-FU							
Hamouda 2001	Prospective cohort of XP patients with multiple facial SCCs (N=10)	BD topical application. Mean treatment duration 6 months (2-36)	7/10 superficial regression. Of 5 patients biopsied post-treatment, 1 had no residual tumour, 4 had persistent tumour in deep dermal layer	Every 2 months. Mean not specified	-	Well tolerated, some cases of pruritus with erythema	8/10 crust disappearance and tumour decrease. 4/10 improved QoL

Litwin 1972	Prospective cohort (33 patients with 53 SCCs)	Topical 5-FU (5%,10% or 20%), od or bd. Av treatment time 10.2 weeks (5-37). 79.2% had 1 course, 17% 2 courses, 3.8% 3 courses	42/53 (79%) complete post-treatment regression (64% confirmed histologically). 8/53 (15%) partial regression. 3/53 (6%) progression of SCC	Average 23.2 months (3-48)	None in those free of disease at least 1 year after completion of treatment	Pain in lesions overlying cartilage	-

There was one prospective multi-centre pilot study (23 patients) which evaluated intratumoral 5-FU, with histologically confirmed clearance in 22 patients (96%) 16 weeks post treatment (Kraus et al., 1998b). Recurrence was not assessed. A case report of intralesional 5-FU reported no recurrence 5 months after treatment (Morse et al., 2003).

One series of 33 patients with 53 SCCs reported complete post-treatment regression of tumour in 42 SCCs (79%) treated with up to three courses of 5%, 10% or 20% topical 5-FU, of which 27 (64%) were confirmed histologically. The remaining SCCs regressed partially (15%) or progressed (6%). No recurrences were observed in those who were disease-free at least 1 year after treatment (Litwin et al., 1972). Another series which only included patients with xeroderma pigmentosum reported superficial regression in 7 of 10 patients with multiple SCCs, although the number of lesions assessed was not specified. Residual tumour remained in the deep dermal layer in 4 of 5 patients biopsied and recurrence was not assessed. Four of the ten patients reported improved quality of life, although this was not formally assessed (Hamouda et al., 2001).

None of the studies reported deaths attributable to SCC.

Cosmetic outcome was reported in one study of intralesional 5-FU, with physicians rating cosmetic outcome as good to excellent in 91% of cases, slightly lower than the 100% good to excellent rating of patients (Kraus et al., 1998b). This study reported superficial erosions in 19 of the 23 (83%) patients, and necrosis in 9 (39%), which cleared after several weeks, plus local temporary alopecia around scalp lesions. No systemic adverse events were noted in any of the studies.

Interferon

There were four case series that reported outcomes after intralesional administration of interferon at varying total doses (Edwards et al., 1992, Wickramasinghe et al., 1989, Ikic et al., 1995), (Kim et al., 2004), the details of which are summarised in Table 11.

Table 11: Studies and outcomes after interferon

Study	Type of study (N=eligible patients)	Dose	Initial response	Follow-up	Recurrence	Adverse events	Cosmesis
Edwards 1992	Prospective multicentre open label trial, 27 SCCs in actinically damaged skin	Intralesional IFN-alfa-2b, as many injections of 1.5 million units as required to blanch tumour & small margin of normal looking skin 3x per week/9 treatments	24/27 (88.9%) histological clearance	18 weeks (site excised)	-	65% (of all 48 in trial) had >1 AE – myalgias, headache, fever. Rigors, flu-like symptoms. 10% severe AE causing interruption of daily activity but none dangerous or long-lasting. 14.6% mildly ↑ LFTs. 6.2% ↓ granulocyte count. 4.2% ↓ platelet count	Patient assessed: 76.9% excellent, 15.4% very good, 3.8% good, 3.8% satisfactory, 0% poor. Clinician assessed: 76.9% excellent, 15.4% very good, 7.7% good, 0% satisfactory, 0% poor.
Wickramasinghe 1989	Prospective series, 3 patients with SCC, lower leg	Intralesional recombinant IFN-α_2 0.9 million units 3x per week/3 weeks	3/3 Complete clinical response confirmed histologically	3 months	-	Transient local discomfort at site. Depressive mood in 1 of total of 19 patients in series	-

Ikic 1995	Retrospective (?) series, 28 patients with eligible SCCs	a) Human natural leucocyte IFN (HNLI) 400,000-1.2 million units/12-13 applications/3-6 weeks. Total 5.6-21.6 million units *or* b) Recombinant IFN-α_{2c} (rIFN) 2-5 million units/20 applications/4 weeks. Total 40-100 million units.	a) 'Complete response' in 32 of 52 patients (all SCCs in series). Unclear if remainder were partial/non responders and what became of them. b) Initial response not reported for rIFN treated	Unclear	a) 1/24 (ear SCC at 4 years) b) 0/4 over 3-7 years	-	-
Kim 2004	Case series including 1 patient with ear SCC	Intralesional IFN-α_{2b} 2 million units/3x per week/3 weeks. Total 18 million units	-	23 months	No recurrence	Influenza-like symptoms, short-term neurologic effects (dizziness, parasthaesia, weakness, confusion, dysarthria, short-term memory loss. Depression at higher doses, transiently elevated LFTs, reversible dose-related bone marrow suppression.	-

The largest prospective multi-centre series reported histologically confirmed clearance in 24 of 27 (89%) SCCs in actinically damaged skin, but did not assess recurrence as the site was excised after 18 weeks (Edwards et al., 1992). A small prospective series observed histologically confirmed clearance at 3 months in all three included patients with lower leg SCCs, but again recurrence was not assessed (Wickramasinghe et al., 1989). One case series (Ikic et al., 1995) reported recurrence of an ear SCC 4 years after treatment with human natural leucocyte IFN in one of 24 patients, although it was unclear how many patients had appeared to respond initially to treatment and what became of those who failed to show a complete response. No recurrence was seen after 23 months in the one patient with an ear SCC who was included in a series of NMSCs treated with intralesional IFN (Kim et al., 2004).

None of the included studies reported on deaths attributable to SCC.

One study evaluated cosmetic outcome, with both patients and clinicians rating the appearance as excellent or very good for 93% of lesions treated, and the remainder being rated as either good or satisfactory (Edwards et al., 1992).

Adverse events were described in three studies (Edwards et al., 1992, Wickramasinghe et al., 1989, Kim et al., 2004) , with flu-like symptoms and transient derangement of liver function being the most commonly reported events. Depression of mood and reversible dose-related bone marrow suppression were also reported. Severe adverse events causing disruption of daily activity were reported in 10% of all 48 patients treated in 1 study, although none were dangerous or lasting (Edwards et al., 1992).

Retinoids

Oral 13-cis-retinoic acid (0.3-0.5mg/kg/day) was administered with calcitriol (1,25-dihydroxyvitamin D_3) (0.5-1 microgram/day) for 3 to 14 months in a prospective series which included six patients who between them had 27 previously untreated histologically proven SCCs at various sites and who were

selected on the basis of them being unsuitable for standard local therapy due to the multiplicity of their lesions and their location (Skopinska et al., 1997). Treatment was stopped at 3 months in one of the six patients due to lack of response. One patient had 'complete regression' (assessed by clinical reduction in lesion size but not assessed histologically) of their three SCCs at 15 months, and the remaining four patients had partial reduction in tumour size of between 30 and 85% although it was unclear at what time point this response was assessed and some of patients had remained on treatment. All patients treated had mild skin and mucosal reactions, with more pronounced inflammation and crusting of the scalp in three male patients which improved with antibiotic ointment. Two patients also had a transient slight increase in serum triglycerides, and two others had a transient increase in urine calcium, all of which resolved when the dose was decreased. No SCC-related deaths were reported.

There was one case report of the use of single agent oral isotretinoin (13 cis-retinoic acid) given at a dose of 2mg/kg/day for 6 months in a patient with multiple cutaneous SCCs of the legs (Levine et al., 1984). Although the number of treated lesions was not specified accurately, one lesion of 'approximately' 20 SCCs remained after 6 months and was reported as a keratoacanthoma when examined microscopically after excision. None of the regressed lesions recurred during the 36 months after treatment, although three new SCCs arose in previously unaffected areas. There was no mention of adverse events in this study.

Other treatments

Cetuximab

We found one case report of the use of cetuximab (a monoclonal antibody which binds to the epidermal growth factor receptor [EGFR]) in combination with γ-irradiation to treat a large unresectable 12cm SCC of the temple (Goppner et al., 2010). Cetuximab was given 24 hours pre-irradiation at a dose of 400mg/m^2 and in 200mg/m^2 infusions at weekly intervals throughout

the irradiation (total radiation dose 45Gy). By 4 weeks post treatment the tumour was regressing, and although histologically confirmed tumour was still present at 8 months it had decreased in size to 0.2 x 1.0cm and was excised surgically, with no evidence of further spread 14 months after treatment. The treatment was well tolerated with a follicular-pustular exanthema which healed quickly with corticosteroid therapy.

Combination systemic treatments

Treatment of eligible SCCs with various combinations of drugs was described in five studies (Fujisawa et al., 2006, Olieman et al., 1999, Sadek et al., 1990, Sheen et al., 2003, Tantranond et al., 1992). These were generally small case series with only a small number of patients with eligible SCCs, or case reports, and are summarised in Table 12. In all of the studies definitive initial treatment with surgery or radiotherapy was not possible. Different chemotherapy regimens and modes of administration were used in each study, with follow-up ranging from 8 months to over 7 years. One study reported limb salvage in two patients after hyperthermic limb perfusion with chemotherapy, with amputation in a third patient with progressive disease after treatment (Olieman et al., 1999). Of three patients with SCCs of disfiguring size who were treated with neoadjuvant chemotherapy prior to surgery, complete response was seen in two patients, although one of them had a local recurrence of tumour after 8 months, and no response was seen in one patient who died from their disease 10 months after treatment(Sadek et al., 1990). No recurrences or metastasis were reported in the remaining studies, although these were all single case reports (Fujisawa et al., 2006, Sheen et al., 2003, Tantranond et al., 1992). All of the studies reported adverse events related to chemotherapy. Two treatment related deaths were reported: one of 15 patients had multiorgan failure after hyperthermic isolated limb perfusion (Olieman et al., 1999), and one of 14 died from a pulmonary infection superimposed on lung fibrosis following neoadjuvant chemotherapy (Sadek et al., 1990).

Table 12: Studies and outcomes combined chemotherapy regimens

Study	**Type of study (N=eligible patients)**	**Treatment details**	**Outcome**	**Follow-up**	**Adverse events**
Fujisawa 2006	Case report (76 year old, non-metastatic SCC of cheek, complete resection too difficult)	IV **cisplatin** 4mg/m^2/day on days 1-5, plus **5-FU** 400mg/m^2/day for 7 days, with concurrent **external beam RT** 2Gy/day 5x per week, total dose 64Gy	No recurrence or metastasis during follow-up	5 years	Mild grade 1 myelosuppression. Ulcer resolving within 3 months
Olieman 1999	Prospective series (3 patients with locally advanced eligible SCCs of limbs, curative resection not possible without severe mutilation or impaired function)	Hyperthermic isolated limb perfusion – subcut **rIFNγ** 0.2mg od for 2 days prior to 90 min infusion of 0.2mg IFNγ plus 3mg (arm) or 4mg (leg) of **TNFγ** & 10-13mg/l **melphalan** under 39-40^{0}C hyperthermic conditions with excision at 6-8 weeks if possible	1/3 complete response (no viable tumour cells); 1/3 partial response; 1/3 local progressive disease and regional disease at 2 months post treatment (then unavailable for follow-up) **Limb salvage** in 2 patients with complete or partial response. Amputation in patient with progressive disease.	Mean 43 months for 2 patients available for follow-up	Multiorgan failure, deep infection, septic shock and death in 1 of all 15 patients. 1/15 superficial wound infection
Sadek 1990	Prospective series (3 patients with eligible SCCs of disfiguring size)	Neoadjuvant chemotherapy: **cisplatin** 100mg/m^2 day 1, **5-FU** 650mg/m^2 by continuous IVI during 5 days, **bleomycin** 15mg IV day1 then 16mg/m^2/day continuous IVI during 5 days. Repeated every 3-4 weeks for 2-3 cycles. Followed by surgery or	2/3 complete response, 1/3 no change (DoD at 10 months). Local recurrence after apparent CR in 1/2 at 8 months. disease in 1	8,10 and 22+ months	Pulmonary infection superimposed on fibrotic lung and death in 1 of all 14 patients. Nausea and vomiting in all patients. Grade 3/4 haematologic

		interferon (not specified when in relation to chemo)			abnormalities in 4/14. Transient trophic and pigmented bleomycin related skin changes.
Sheen 2003	Case report (SCC big toe, amputation refused)	Intra-arterial **MTX** 50mg/d infusion for 8 days plus IM **leucovorin** 6mg 6hourly for 8 days, then intermittent arterial infusion of 50mg of MTX weekly until wound healed	Complete response 2 months after start of treatment (mass disappeared). No recurrence during follow-up	7 years 3 months	Generalised skin rash and grade 1 itch
Tantranond 1992	Case report (SCC of pinna, surgery not indicated as bone involvement, RT doses prohibitive	**Topical 5-FU** plus IV **cisplatin** 60mg/m^2 on d1 plus IV 5-FU d1-4 plus oral **isotretinoin** 50mg/bd. 6 cycles in total every 28 days	No evidence of residual SCC after 5^{th} course. No recurrence during follow-up	2.5 years	Isotretinoin discontinued after 60 days due to severe cheilitis

4.5 Discussion

Despite the high burden associated with the treatment of SCC, the evidence base for the different treatment modalities is limited. The Cochrane systematic review of treatments for primary, non-metastatic cutaneous SCCs has shown the lack of high-quality data from randomised controlled trials (chapter 3). This systematic review of observational studies was therefore conducted in order to review the evidence for different treatments, to help inform management guidelines, and to provide information relating to the outcome rates for different treatments to aid in the development of future clinical trials to assess the effectiveness of selected treatment(s).

4.5.1. Overall summary of the results and clinical implications

Caution needs to be exercised when comparing outcomes after different treatment modalities due to the limitations of the included studies discussed in the introduction. Additionally overlapping confidence intervals for average effect estimates for the different treatments suggest that apparent differences between treatments may not be significant. Results for the main treatment modalities are summarised in Table 13.

Surgery with a predefined excision margin is the treatment of choice for the majority of cutaneous SCCs, with MMS being recommended for SCCs considered to be higher risk or in cosmetically sensitive areas. The pooled analysis suggests lower local recurrence rates and deaths attributable to disease after MMS; despite the fact that tumours treated by this method are likely to be higher risk although there have been no RCTs to directly compare the two treatments. However, using pooled analysis, regional recurrence was of a similar magnitude for both treatment modalities, which may be suggestive of subclinical spread of some higher risk tumours treated with MMS to regional lymph nodes at the time of treatment.

Table 13: Summary of SCC treatments

Intervention	Local recurrence (%)	Regional recurrence (%)	Unspecified recurrence (%)	Death attributable to SCC (%)
Surgical excision	5.4 (2.5 to 9.1); 12 studies, n=1144	4.4 (2.4 to 6.9); 8 studies, n=786	5.8 (0.7 to 27.6); 2 studies, n=113	4.1 (1.7 to 7.6); 8 studies, n=485
Mohs micrographic surgery	3.0 (2.2 to 3.9); 10 studies, n=1572	4.2 (2.3 to 6.6); 6 studies, n=1162	4.7 (0.7 to 11.7); 5 studies, n=766	1.1 (0.2 to 2.6); 4 studies, n=941
External radiotherapy	6.4 (3.0 to 11.0); 7 studies, n=76	2.6 (0.04 to 8.9); 3 studies, n=272	4.8 (0.6 to 12.8); 6 studies, n=220	9.1 (1.4 to 22.8); 5 studies, n=191
Brachytherapy	5.2 (1.6 to 10.5); 6 studies, n=88	—	—	—
ART: PNI	18.2 (3.8 to 39.8); 5 studies, n=22	8.3 (1.1 to 21.4); 5 studies, n=22	—	11.1 (0.4 to 33.1); 4 studies, n=20
ART: Non-PNI	11.1 (2.4 to 25.0); 4 studies, n=47	8.5 (2.5 to 17.6); 4 studies, n=47	—	14 (0.04 to 50.2); 3 studies, n=21
Cryotherapy	—	—	0.8 (0.1 to 2.2); 8 studies, n=273	—
Curettage and electrodesiccation	—	—	1.7 (0.5 to 3.4); 7 studies, n=1131	—
Photodynamic therapy	—	—	26.4 (12.3 to 43.7); 8 studies, n=119]	—

In the pooled analysis of external radiotherapy, average local recurrence was slightly higher than that seen after conventional surgical excision, although the differences are probably not significant with overlapping confidence intervals. Interestingly the odds of regional recurrence were lower, although this data was generated from just two studies (Barysch et al., 2012, Tsao et al., 2002) with other studies not specifying whether the recurrences they reported were local or regional failures, so the true significance of this is unclear. The lower local recurrence rates from the studies in which brachytherapy was used may be a reflection of the more superficial, lower risk nature of the included SCCs treated by this method, although patients numbers were generally small and limited follow-up of only a few months in some of the studies may be inadequate to detect later recurrences.

The greater rates of recurrence, metastasis and death from disease observed with adjuvant radiotherapy after surgical excision is in accordance with other studies (Jambusaria-Pahlajani et al., 2009), although numbers in included studies were small and for non-PNI SCCs the reasons justifying the use of ART were not always clear. The results may therefore be a reflection of selection of those SCCs with a particular poor prognosis, and the identification of prognostic factors which may benefit from ART remains an area of uncertainty and one in which prospective studies are required.

Lowest recurrence rates were observed after cryotherapy and ED&C respectively, but the majority of SCCs included in these analyses were small and considered to be low-risk lesions but the evidence is poor to advocate its use in lesions considered at higher-risk of recurrence and recurrent SCCs.

Based on the results in this systematic review, the use of PDT to treat invasive SCCs cannot be advocated. Few studies confirmed histological clearance in apparently completely responsive SCCs, and in those which attempted to do so, residual tumour remained in a number of biopsies. Furthermore, more

than a quarter of those tumours which had appeared to completely respond to PDT initially recurred during follow-up.

Not all patients with SCC are amenable to surgical treatment or radiotherapy and some people are susceptible to multiple SCCs as a result of a genetic or immune predisposition. Such groups pose particular therapeutic challenges, and there is a growing need for effective topical or systemic agents which could be used in such cases. The current evidence for these agents to treat primary SCCs is largely anecdotal, based on single case reports or very small numbers of eligible patients in open-label trials with limited follow-up and generally lacking recurrence data, but is an interesting area for further development as new insights into the pathogenesis and targeted therapies emerge.

Although quality of life was one of the outcomes in this review, none of the included studies measured this. Patient Reported Outcome Measures (PROMs) have great potential to improve the quality of health services by providing validated evidence of health from the patient's perspective. Two recent systematic reviews of PROMs in skin cancer showed that there have been limited evaluations of PROMs specifically designed for patients with nonmelanoma skin cancers, and furthermore that the questionnaires developed so far are not perfect for assessment of quality of life in these particular patients (Gibbons et al., 2013, Bates et al., 2013). Nevertheless, the incorporation of patient reported outcomes will undoubtedly be important in the development of future clinical trials comparing treatments for SCC, and should be able to capture quality of life issues which are important to patients with this condition, including detailed assessment of cosmetic and functional outcomes at specific time points.

4.5.2. Bias and quality of reporting

Poorly reported studies can lead to discrepancies between data extractors and hinder assessment of the risk of bias. The majority of the studies in this review were published before the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (Vandenbroucke et al., 2007) of 2007 which was introduced with the aim of improving the quality of reporting of these types of studies, using similar principles to the CONSORT (Consolidated Standards of Reporting Trials) checklist (Schulz et al.) for RCTs. Just one study (Brantsch et al., 2008), which we assessed to be of good reporting quality, declared overtly that STROBE guidelines had been followed.

Most of the included studies were of limited methodological quality and prone to bias (Figure 19), with variable patient mixes in terms of prognostic factors, overall disease severity and duration of follow-up. Recruitment bias with selection of particular treatment modalities based on tumour or patient characteristics is a serious consideration for case series and was positively identified or was an unclear risk in 85% of the studies in this review, making it impossible to directly compare the effectiveness of different treatments.

In 41% of studies, losses to follow up were either incompletely reported or were not mentioned at all in which case it was difficult to assess the risk of attrition bias. None of the studies included in this systematic review had blinded assessment of outcomes which is a potential source of reporting bias. However, by considered planning in advance it should be feasible to introduce an element of blinding to prospective case series, for example by having personnel collect data on patient and tumour characteristics independently from those assessing outcome so that the latter have no prior knowledge of these characteristics (Kooistra et al., 2009).

At present, there is no requirement for registration of non-randomised studies, the presence of publication bias is more difficult to assess than for RCTs, but is assumed to be present and is drawback in this kind of systematic

review. A survey of published case series and reports revealed that 79% reported only treatment success, 10% reported treatment failures as well as successes but only 10% reported treatment failures (Albrecht et al., 2005).

4.5.3. Stratification of risk

A limited number of studies stratified outcomes according to particular prognostic indicators, although in the majority of studies it was not possible to stratify results from data provided. Ear location as a poor prognostic feature is supported by the pooled analysis of data from studies in which ear and other locations were considered separately. A pooled analysis of other features considered high-risk was not conducted due to different reporting methods in the studies in which these factors were considered.

Increased risk of recurrence with tumours greater than 2cm was noted in some of the included studies (Pless, 1976, Cherpelis et al., 2002, Griffiths et al., 2002), although this finding was not supported by Mourouzis (Mourouzis et al., 2009) with 60% of metastases originating in SCCs smaller than 2cm, nor by Dzubow (Dzubow et al., 1982) who found a trend towards significance with tumours larger than 5cm in diameter.

Several studies showed the importance of SCC depth as a risk factor for recurrence. No metastases were observed in SCCs less than 2mm in depth by Mourouzis (Mourouzis et al., 2009), in accordance with Brantsch (Brantsch et al., 2008) who reported a significantly increased risk of metastases for SCCs greater than 2mm thick. Griffiths (Griffiths et al., 2002) also reported a significant difference in thickness between SCCs in patients who died of their disease and those who did not.

Poor differentiation was noted to be an adverse prognostic feature in two of the included studies (Cherpelis et al., 2002, Mourouzis et al., 2009), with the presence of PNI being significantly associated with a worse outcome in one of the series (Cherpelis et al., 2002).

4.5.4. Strengths and limitations of this Systematic Review

The combined systematic reviews described in this chapter and in chapter 3 are the first systematic reviews to assess the effectiveness of all treatment modalities for primary non-metastatic SCC. This systematic review is the first to focus on non-randomised studies of SCC treatments.

Although much effort was made to ensure that the literature search was as thorough as possible, it is inevitable that some relevant studies were missed. The Medline and Embase databases were searched, but it is possible that there were relevant studies in other databases that were not searched. Observational studies, and especially case series, are less easy to identify from searching literature databases than RCTs; usually they are not identifiable from the title and are less consistently indexed according to study design in bibliographic databases. Searches that are sensitive enough to detect case series generally lack specificity making it likely that some studies are not identified (Dalziel et al., 2005). Many of the studies identified in the review were identified after scrutinising reference lists. The search was limited to those published in English, in part due to the large number of studies, but also as the translation of studies which are generally only of limited reporting quality could introduce an additional source of bias.

The treatment of recurrent SCCs and tumours known to be metastatic at presentation was not addressed in this systematic review. Many studies have been excluded as they included previously treated relapsed tumours without separation of data from non-recurrent tumours. Such recurrent tumours may have different features to those which have not been treated previously which makes them more likely to recur or resistant to treatment.

Similarly, studies relating solely to the management of SCC in solid organ transplant recipients were not specifically searched for, although some of the studies did include such patients. Cutaneous SCC is an important cause of

morbidity in this group of patients, associated with the likelihood of multiple tumours and with a potentially more aggressive clinical course (Zwald and Brown, 2011). It is therefore perhaps a subject suitable for separate consideration and beyond the scope of this more general review.

4.5.5. Implications for future research

There is plenty of scope for further research to improve the evidence base for SCC treatments, ideally with the development of well-designed adequately powered RCTs which are currently lacking. The relationship between different prognostic features is difficult to assess from the evidence currently available yet is important in order that stratification according to risk can be made and treatment decisions based upon this. Outcomes for future trials should be standardised, with consistent follow-up at one years and two years and with a minimum follow-up of at least 5 years. An intention-to treat approach, in which all participants are analysed according to the initial treatment group allocation irrespective of actual treatment received and whether there was cross-over, full-compliance or drop-out, is regarded as the least biased method to estimate treatment effects in RCTs and to deal with attrition of participants (Newell, 1992). However, the intention-to-treat approach is often inadequately described and applied by trialists and recommendations have been made for the design, conduct, analysis and reporting of trials to address such issues and assist researchers to design trials and readers to interpret the validity of their results (Hollis and Campbell, 1999). This should include minimisation of incomplete outcome data, with description of how missing data will be handled and investigation of the possible effects of missing data. A multidisciplinary approach to running such future trials should be encouraged, as these tumours present across a variety of specialties and their management is frequently co-ordinated by a specialist multi-disciplinary team.

4.6 Conclusion

Cutaneous SCC is one of the most common cancers in humans and presents a significant public health impact, yet the evidence base for the treatment of SCC is poor. It is not possible to compare treatment outcomes accurately from the available evidence and there is a need for targeted research to identify which patients will benefit from most from particular treatment strategies. This systematic review has complemented the Cochrane systematic review that has been described previously (Chapter 3) by providing a thorough appraisal of the treatments of cutaneous SCC. Furthermore, it has provided information on event rates for different treatments for a range of clinically important outcomes, and highlighted deficiencies common to many of the published studies, such as a lack of patient-reported outcomes and detail about prognostic features, which will need to be taken into account when designing any future clinical trials involving interventions for SCC.

CHAPTER 5: SURVEY TO IDENTIFY TREATMENT UNCERTAINTIES

5 SURVEY TO IDENTIFY TREATMENT UNCERTAINTIES

5.1 Abstract

Objectives: This survey was conducted in order to inform the development of a proposal for an RCT of cutaneous squamous cell carcinoma (SCC) treatments. The objectives were: to gain an overview of current treatment practices among healthcare professionals (HCPs) treating patients with SCC; to identify clinically important areas of management uncertainty among HCPs; to give this group the opportunity indicate their interest in involvement in and to suggest topics for a future RCT.

Methods: An online survey was sent to a multidisciplinary group of healthcare professionals having an interest in skin cancer treatment and research. Professional organisations of which such people were likely to be members identified and distributed the surveys (British Society of Dermatological Surgery; British Association of Plastic, Reconstructive and Aesthetic Surgeons; Royal College of Radiologists Site Orientated e-Network; and UK Dermatology Clinical Trials Network). The online surveys sought to gather data on current treatment practices, including biopsy and follow-up. Participants also had the opportunity to identify areas of treatment uncertainty, to suggest which treatments should have their effectiveness assessed in the form of an RCT, and to indicate which core outcome measures should be used to assess the effectiveness of treatments. The potential willingness of those taking part in the survey to be involved in a future RCT was also evaluated.

Results: 1820 HCPs were sent or had to access to the survey, of whom 306 responded (17%). The vast majority of respondents (97%) treated SCC by surgical excision with a predetermined margin. 12.3% of respondents were also able to perform Mohs micrographic surgery. All 6 of the clinical oncologists who responded treated SCC with radiotherapy either alone or as an adjunct after surgery. Apart from the clinical oncologists who always perform pre-treatment biopsies, biopsies are rarely performed or are only

done in 25-50% of cases. Almost three-quarters of respondents would follow-up a patient with high risk SCC for a minimum of 2 years, whereas more than half of them would follow-up patients with low-risk SCCs for less than 1 year. Optimisation of surgery and the role of radiotherapy and newer agents were identified as areas where there is a need for more research, with survival and loco-regional recurrence being identified as the most important outcomes to assess. Specific areas of uncertainty related to optimal excision margins, the role of adjuvant radiotherapy, ideal follow-up regimens and the lack of a prognostic model for survival and recurrence.

Conclusions: This online survey identified areas of SCC treatment uncertainty among HCPs and generated suggestions for possible future research. It also identified what HCPs consider to be the most important outcome measures s in such a trial. Through the identification of which treatments should have their clinical effectiveness assessed, the results from the survey have informed and contributed to the wider body of feasibility work that has been undertaken in this research towards the development of future research.

5.2 Introduction

Surveys are well-established in healthcare research as tools for obtaining data on healthcare practices, the organisation of care, and knowledge and attitudes among providers.

This chapter describes an online electronic survey of healthcare professionals (HCPs) involved in cutaneous squamous cell carcinoma (SCC) management which was conducted to gain insight into current treatment practices, and to identify areas where HCPs feel more research is required in order to answer clinically important treatment uncertainties which they feel are not answerable from the current evidence base.

5.2.1. Why it was important to conduct this survey

The appraisal of the evidence base for the efficacy of treatments for SCC is poor, as has been discussed in earlier chapters of this thesis (chapters 3 and 4), being largely based on case series. Currently, no published data from randomised controlled trials are available comparing treatments for the types of SCC that are seen in routine clinical practice. Given the enormous service burden of treating non-melanomas, the need for large, prospective studies to compare different treatments has been recognised as a research priority in the UK (Motley et al., 2002, National Institute for Health and Clinical Excellence, 2006).

The treatment of SCC is undertaken by a wide range of clinicians; dermatologists, plastic surgeons, clinical oncologists, and surgeons of several disciplines such as general, ENT, maxillofacial and ocular surgery. Although it is not recommended that general practitioners should definitively treat SCCs themselves (National Institute for Health and Clinical Excellence, 2006), they have an important role to play in diagnosing and urgently referring cases of suspected SCC to a specialist member of the local skin cancer multidisciplinary team (LSMDT) or specialist skin cancer MDT (SSMDT). Therefore, as the management of SCC is frequently multidisciplinary, this survey was designed to canvas a wide range of practitioners who have an interest in SCC treatment

and was conducted as part of the background feasibility work towards furthering research in this area. Assessment of adherence to current clinical guidelines was not one of the objectives of the survey.

5.2.2. Objectives of this survey

The objectives of this survey were to:

- gain an overview of current SCC treatment practices
- invite HCPs to suggest potential research topics on SCC treatment, as a guide for future discussions regarding the development of an RCT trial proposal
- offer clinicians the opportunity to express their interest in taking part in a future clinical trial

5.3 Methods

The vast majority of SCCs are treated by dermatologists, plastic surgeons or clinical oncologists. Prominent professional bodies for these specialties were identified as points of distribution for the survey, namely:

- The British Society for Dermatologic Surgery (BSDS), representing dermatologists who carry out skin surgery;
- The British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS), the membership of which is mainly plastic surgeons but with some members from other surgical specialties;
- The skin Site Orientated e-Network (SOeN) of the Royal College of Radiologists, a subgroup of clinical oncologists with an interest in skin cancer;
- The UK Dermatology Clinical Trials Network (UKDCTN), a mixed group of dermatologists, GPs, clinical nurse specialists in dermatology, and patients, all of whom have an interest in promoting research in dermatology.

The survey was cross-sectional (administered at one time point) and developed in an electronic format using the Survey Monkey professional on-line tool (www.surveymonkey.com). Four different versions were generated, one for each of the targeted professional bodies. Although all four surveys sought answers to similar questions, each one was developed with one or more members from each of the groups to ensure that the questions were relevant to that particular group. The main structural difference between the surveys related to the question regarding primary management of SCC.

Approval of each survey was obtained from the President of the BSDS, the Executive Committee of BAPRAS, and the President of the Royal College of Radiologists. Surveys were piloted by members of the Centre of Evidence Based Dermatology to test the functionality of the on-line format. Each survey was presented over seven pages, with one to four questionnaire items per page. Respondents were able to review and change their answers before submitting. A copy of the survey sent to UKDCTN members is attached in Appendix 3.

Between January and March 2010, each professional organisation sent an e-mailed invitation letter and web link to the corresponding electronic survey to members on their distribution list (BSDS, BAPRAS, UKDCTN), or posted it on the specialist group website (SOeN). The invitation letter explained the purpose of the work, approximately how long the survey would take to complete, and reassured participants of the anonymity of their responses. For the UKDCTN survey, potential participants were asked not to complete the survey if they had already taken part via one of the other organisations surveyed. The survey could only be accessed once from a particular IP address, in an attempt to prevent duplicate entries. Completion of the survey was voluntary, with no incentives offered. Surveys remained open for responses for three weeks, a reminder being sent to members via each organisation one week prior to closure. Responses were analysed from both completed surveys and those that were terminated early (i.e. the respondent did not complete all the questionnaire pages). Raw data were exported into an Excel spreadsheet to allow simple statistical analysis of percentages and means and generation of graphical representations. Free-text responses were analysed manually. Response rates were calculated by dividing the number of people who were sent the link to the survey by the number who started it, multiplied by 100. Completion rates were calculated by dividing the number who started the survey by the number who completed it, multiplied by 100. A 'Checklist for Reporting Results of Internet E-Surveys' (CHERRIES) was used for reporting the results of the survey (McAlister et al., 2003)(Table 14).

Table 14: Checklist for reporting results of internet surveys (McAlister et al., 2003)

Category	Checklist item
Design	• Survey design
Institutional Review Board approval	• IRB • Informed consent • Data protection
Development and pre-testing	• Development and testing
Recruitment process	• Open versus closed survey • Contact mode • Advertising survey
Survey administration	• Web/e-mail • Context (description of site) • Mandatory/voluntary • Incentives • Time/date • Randomisation of items • Adaptive questioning • Number of items • Number of screens • Completeness check • Review step
Response rates	• Unique visitor site (e.g. based on IP address) • View rate • Participation rate • Completion rate
Preventing multiple entries from one individual	• Cookies used • IP check • Log file analysis • Registration
Analysis	• Handling incomplete questionnaires • Questionnaire submitted with atypical timestamp (i.e. didn't take long enough to complete) • Statistical correction

5.4 Results

From a total of 1820 people who received the survey, 306 (16.8%) attempted the survey, with 255 answering all the questions (Table 15).

Table 15: Response rates of organisations surveyed

Organisation	Number receiving survey	Number attempting survey (response rate %)	Number attempting survey who answer all the questions (completion rate %)
BSDS	250	70 (28.0)	63 (90.0)
BAPRAS	851	138 (16.2)	110 (79.7)
SOeN	249	6 (2.4)	5 (83.3)
UKDCTN	470	92 (19.6)	77 (83.7)
Overall	**1820**	**306 (16.8)**	**255 (83.3)**

BSDS = British Society of Dermatological Surgeons; BAPRAS= British Association of Plastic, Reconstructive and Aesthetic Surgeons; SOeN = Site Oriented e-Network of the Royal College of Radiologists; UKDCTN = UK Dermatology Clinical Trials Network

5.4.1. Professional capacity

More than three-quarters of those who responded to the survey were consultants in either dermatology, plastic surgery or clinical oncology (Figure 41), and 82.4% of respondents had been in clinical practice for more than 5 years (Figure 42).

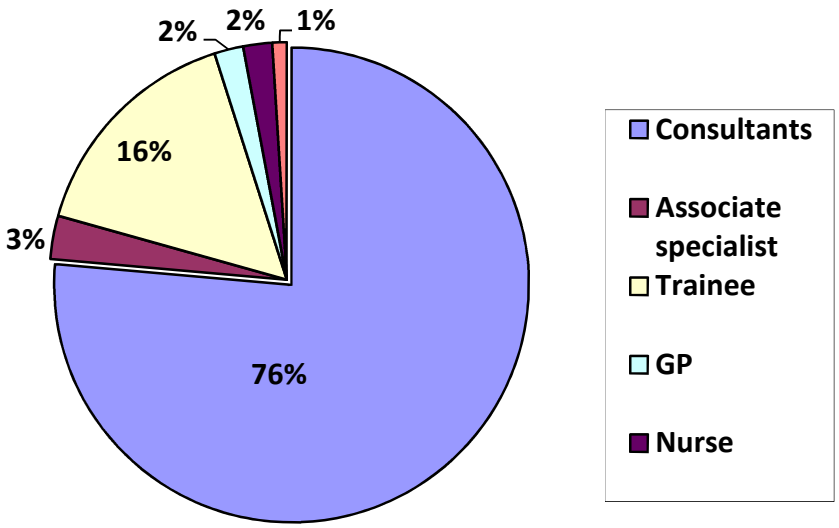


Figure 41: Professional capacity of survey respondents (n=302)

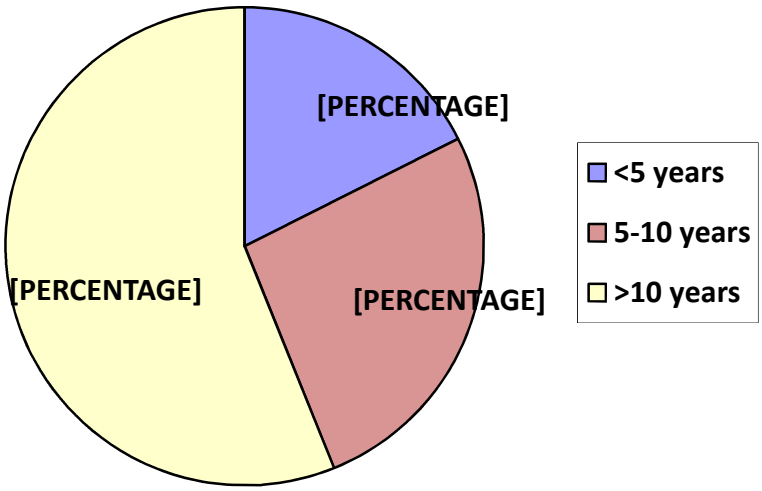


Figure 42: Length of clinical practice of respondents (n=205)

5.4.2. Treatment practices

Based on data from respondents who were able to give a numerical estimate, the average number of SCCs treated annually by members of each organisation is shown in Table 16. A further 41 respondents gave a range for number of SCCs treated, four were not certain and unable to estimate, one was retired, and one was no longer doing skin cancer clinics. Respondents who were members of BAPRAS treated on average 76 SCC patients annually, compared with an average of 65 patients by BSDS members annually, 47 patients for UKDCTN members and 26 patients for the four radiologists who responded.

Table 16: Mean numbers of SCCs treated by respondents over one year

Organisation	Mean number of SCC treated per annum (range; median)
BSDS (n=49)	65 (12 to 400; 50)
BAPRAS (n=92)	76 (0 to 500; 50)
UKDCTN (n=66)	47 (2 to 200; 30)
SOeN (n=4)	26 (8 to 50; 22.5)

BSDS = British Society of Dermatological Surgeons; BAPRAS= British Association of Plastic, Reconstructive and Aesthetic Surgeons; SOeN = Site Oriented e-Network of the Royal College of Radiologists; UKDCTN = UK Dermatology Clinical Trials Network

Overall 260 of 269 (96.6%) of BSDS, BAPRAS and UKDCTN respondents treat primary invasive non-metastatic SCC by attempted single excision with a predetermined margin (98.6%, 98.3% and 92.8% of respondents from these groups respectively). Fewer respondents (33 of 269 [12.3%]) reported being able to offer Mohs micrographic surgery (17.4%, 11.1% and 9.6%, respectively). All the clinical oncologists use either radiotherapy alone or as an adjuvant post operatively, and one also uses chemoradiation (although the numbers who responded to the SOeN survey were only very small so this should not be regarded as representative of the practice of all clinical oncologists). Other treatments sometimes used by members of the BSDS and

UKDCTN include curettage and cautery (some specified for lesions that appear to be low risk, or in the very old and frail), cryotherapy and topical cytotoxic agents. Radiotherapy was also reported to be a treatment used by a few members of these groups, although presumably after discussion with colleagues in their skin cancer specialist MDT and referral to a clinical oncologist.

5.4.3. Biopsy

Most respondents from the BSDS, BAPRAS and UKDCTN reported that biopsies of suspected SCCs are either rarely done, or are performed in only about 25–50% of cases (Figure 43). In contrast, all six of the clinical oncologists who responded stated that they always biopsy pre-treatment.

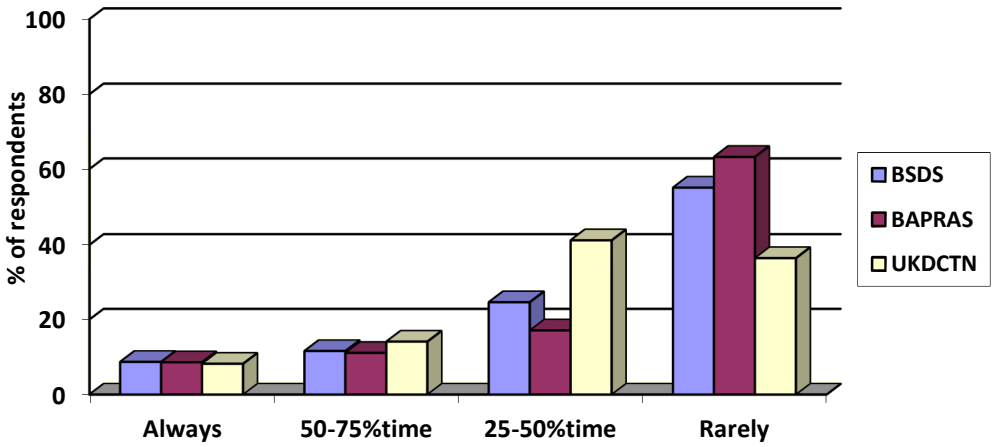


Figure 43: Pre-treatment biopsy rates by professional group

BSDS = British Society of Dermatological Surgeons; BAPRAS= British Association of Plastic, Reconstructive and Aesthetic Surgeons; UKDCTN = UK Dermatology Clinical Trials Network

5.4.4. Follow-up

Almost two-thirds of respondents reported that they would follow up a patient with an SCC they considered to be 'high-risk' for between 2 and 5 years (Figure 44), with a further 9% following them for at least 5 years, compared to only 26% who would follow up for less than 2 years. In contrast,

patients with what respondents considered to be ‘low-risk’ SCCs would be followed up for less than 1 year by 57% of respondents, with a further quarter following them for 1–2 years (Figure 45).

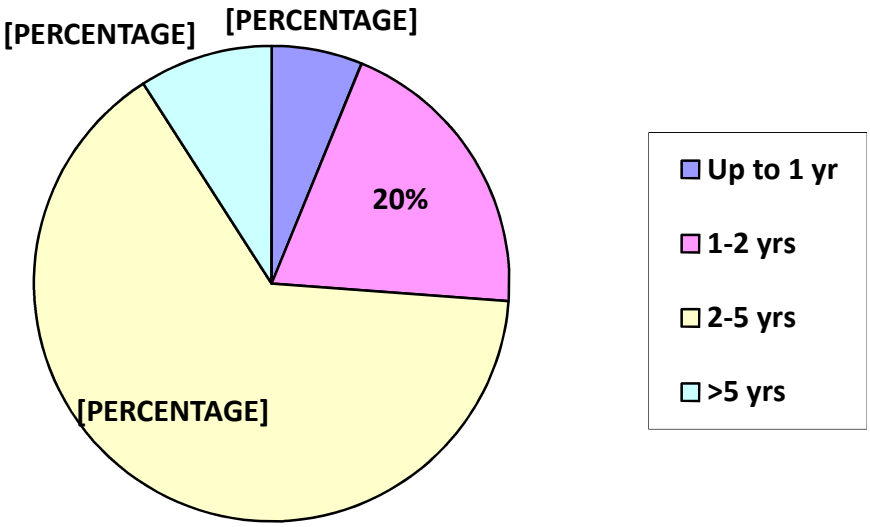


Figure 44: Follow-up of 'high-risk' lesions (n=275)

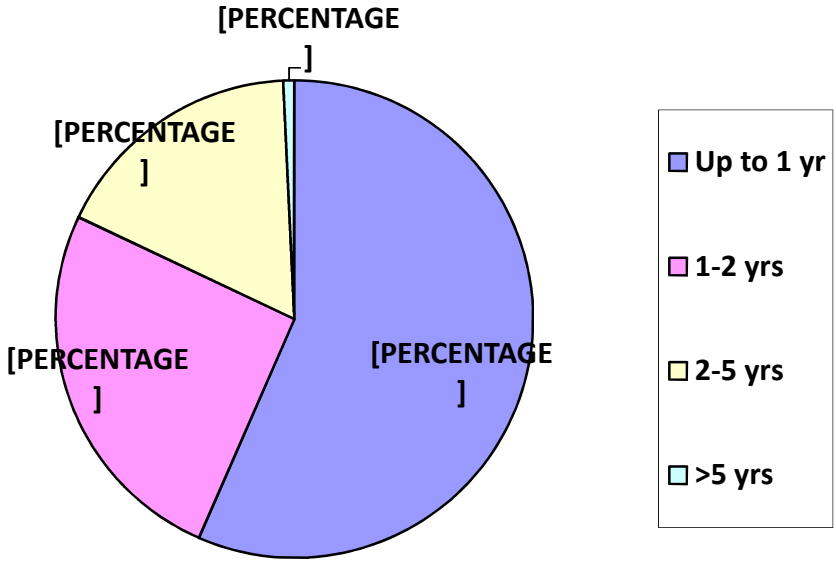


Figure 45: Follow-up of 'low-risk' lesions (n=267)

5.4.5. Research topics

One of the aims of this survey was to identify clinically important management uncertainties, in order to guide the development of ideas for clinical trials to determine the relative effectiveness of the treatments. Based on the pre-specified research categories proposed in the survey, optimisation of surgical treatment, the role of radiotherapy, and the role of newer agents, were the areas in which there was greatest interest (Table 17).

Table 17: Respondents' views on areas of perceived need for clinical trials

Research Category	Number of response to 'Need for a clinical trial' (%)		Total
	Yes	No	
Optimising surgery	181 (75.7)	58 (24.3)	239
Role of radiotherapy	157 (71.0)	64 (29.0)	221
Role of chemotherapy	108 (54.3)	91 (45.7)	199
Role of newer agents	174 (79.4)	45 (20.5)	219
Other	28 (40.0)	42 (60.0)	70

There were some differences in research area priorities between the groups. Optimisation of surgery and the role of radiotherapy were considered the most important areas for research by BSDS members (78.7% and 75.8% respectively). For BAPRAS and UKDCTN members, the role of newer agents (86.7% and 83.9% respectively) and the optimisation of surgery (78.8% and 71.6% respectively) were the top two areas.

In addition, respondents were invited to submit free-text suggestions for specific research questions and other comments relating to a potential clinical trial. Several broad categories could be derived from the responses, and the numbers of responses in each category were counted. Some respondents entered free text which could be split into more than one category, so each free-text comment was subdivided as necessary. The categories identified and distribution of respondents' comments are listed in Table 18.

Free-text replies tended to be general identification of topics for possible research rather than specific ideas for clinical trials. Nonetheless, the top three areas of uncertainty expressed by clinicians, and where there was felt to be a need for more research, were excision margins, the role of radiotherapy for high-risk SCCs or incompletely excised SCCs, and optimal follow-up regimens. There was also recognition of the current lack of a prognostic model upon which to base treatment and follow-up. Although the need for more research into the role of other treatments such as chemotherapy and newer therapies was generally considered to be a research priority, there was a lack of research questions relating to specific agents in the free-text replies.

Table 18: Research topics identified by respondents according to professional body in order of frequency of occurrence

Research topic	BSDS n=26 (%)	BAPRAS n=31 (%)	UKDCTN n=18 (%)	RCR n=3 (%)	TOTAL n=78 (%)
Excision margins	8 (30.8)	12 (38.7)	4 (22.2)	-	24 (30.8)
Role of radiotherapy	8 (30.8)	6 (19.4)	3 (16.7)	3 (100.0)	20 (25.6)
Follow-up	7 (26.9)	7 (22.6)	4 (22.2)	-	18 (23.1)
Prognostic model	1 (3.8)	7 (22.6)	2 (11.1)	-	10 (12.8)
Mohs versus excision	3 (11.5)	2 (6.4)	-	-	5 (6.4)
New agents	1 (3.8)	2 (6.4)	2 (11.1)	-	5 (6.4)
Topical agents	1 (3.8)	2 (6.4)	1 (5.6)	-	4 (5.1)
Curettage versus surgery for low-risk SCC	3 (11.5)	-	1 (5.6)	-	4 (5.1)
Chemotherapy/electro-chemotherapy	-	3 (9.8)	-	-	3 (3.8)
Treatment of immune suppressed/transplant	2 (8.0)	1 (3.2)	-	-	3 (3.8)
Early diagnosis techniques	-	1 (3.2)	2 (11.1)	-	3 (3.8)
Imaging techniques	1 (3.8)	2 (6.4)	-	-	3 (3.8)
PDT	-	2 (6.4)	-	-	2 (2.6)
Sentinel lymph node biopsy	-	2 (6.4)	-	-	2 (2.6)

5.4.6. Core outcomes

The survey also sought to identify which core outcomes were considered to be of greatest importance to clinicians after treatment of SCC (Table 19).

Table 19: Relative importance of post-treatment outcomes, ordered by those considered to be very important

Outcome	Very important (%)	Important (%)	Fairly important (%)	Not important (%)	Total
Survival	**223 (86.1)**	27 (10.4)	7 (2.7)	2 (0.8)	259 (100.0)
Regional recurrence	**224 (85.8)**	34 (13.0)	2 (0.8)	1 (0.4)	261 (100.0)
Local recurrence	**206 (78.9)**	50 (19.2)	5 (1.9)	0 (0.0)	261 (100.0)
Quality of life	**126 (48.6)**	**107 (41.3)**	23 (8.9)	3 (1.2)	259 (100.0)
Persistent ulceration	**108 (42.4)**	**101 (39.6)**	41 (16.1)	5 (1.9)	255 (100.0)
Persistent pain	**103 (40.4)**	**99 (38.8)**	47 (18.4)	6 (2.4)	255 (100.0)
Acceptability to patient	77 (29.6)	**128 (49.2)**	53 (20.4)	2 (0.8)	260 (100.0)
Disfigurement	72 (27.8)	**157 (60.6)**	29 (11.2)	1 (0.4)	259 (100.0)
Contracture	38 (15.2)	**132 (52.8)**	74 (29.6)	6 (2.4)	250 (100.0)
Pain of procedure	20 (7.8)	**95 (37.3)**	**100 (39.2)**	40 (15.7)	255 (100.0)

Almost all of the short- and long-term outcomes suggested (with the exception of pain of procedure) were considered to be 'very important' or 'important' by the majority of those who responded to the question. However, survival and local and regional recurrence were the three outcomes considered to be of greatest importance.

5.4.7. Theoretical willingness to recruit into a future randomised controlled trial for squamous cell carcinoma

Clinicians were asked if they would be prepared to recruit their patients into either a future full-scale clinical trial addressing an aspect of the treatment of SCC, into a feasibility study only, or into both. The results are summarised for each professional group in Table 20. Overall, there was interest in taking part in a full-scale trial amongst 44% of respondents, with a further third indicating that they may be interested in taking part.

Table 20: Hypothetical willingness of clinicians to recruit into an RCT of SCC treatments

Potential willingness to recruit patients	BSDS	BAPRAS	UKDCTN	RCR	TOTAL
Yes, full-scale RCT	32 (52.4)	38 (38.8)	31 (41.9)	4 (100.0)	**105 (44.3)**
Yes, but feasibility study only	2 (3.3)	2 (2.0)	1 (1.4)	-	**5 (2.1)**
No	5 (8.2)	28 (28.6)	16 (21.6)	-	**49 (20.7)**
Maybe	22 (36.1)	30 (30.6)	26 (35.1)	-	**78 (32.9)**
TOTAL	**61 (100.0)**	**98 (100.0)**	**74 (100.0)**	**4 (100.0)**	**237 (100.0)**

5.5 Discussion

Surveys are a useful research tool to elicit practice patterns, behaviours and concerns of physicians (Creel et al., 2005). The purpose of this survey was to gain an overview of how cutaneous SCCs are currently being treated across the UK, and to help identify potential topics for an RCT based on what healthcare professionals consider to be important areas of uncertainty in the management of SCC.

5.5.1. Current treatment practices

Treatment

Several treatment options are available for managing SCCs, and guidance for clinicians is given in multiprofessional guidelines, based upon whether the tumour is considered to be at low or high risk of recurrence and/or metastasis (Motley et al., 2002). From these guidelines, surgical excision is generally the treatment of choice for the majority of SCCs and was undertaken by the vast majority of specialists in this survey, other than clinical oncologists who use radiotherapy. Thirty-three of the 255 respondents (12.9%) were able to offer Mohs surgery, a treatment which may be considered for high-risk tumours and those in functionally sensitive areas. Other treatments such as cryotherapy, and curettage and cautery, which the guidelines state may be indicated for small, low-risk tumours, were also used by respondents although less frequently than surgical options. Topical cytotoxics were also used by 19 respondents (7.4%), although their use is not recommended in the guidelines; evidence in support of their value is very limited and based mostly on single case reports.

Biopsy

Over three-quarters of respondents from BSDS, BAPRAS and UKDCTN replied that they either rarely biopsied before treatment, or only biopsied between 25% and 50% of suspected SCCs. This is perhaps not surprising as surgical excision generates histology anyway. In contrast the clinical oncologists

always biopsied suspected SCCs before radiotherapy. Between 32% and 47% of SCCs may be incorrectly diagnosed prior to surgery (Brown and Lawrence, 2006, Ashby et al., 1989b), and it has been suggested that pre-treatment biopsies may be required in a greater number of cases so that excision may be expedited. Furthermore, lack of histology from destructive treatments such as cryosurgery, or curettage and cautery, may contribute to the under-reporting of SCCs that is recognised in the UK (Alecu et al., 1998). However, it has been estimated that if pre-treatment biopsies were carried out for every skin tumour, there would be a seven-fold increase in the number of tumours assessed (Brown and Lawrence, 2006), which could be prohibitively costly and unfeasible.

Follow-up

Uncertainty about optimal follow-up was raised by 23% of all respondents in this survey. The purpose of follow-up is to identify recurrent and metastatic disease and to identify new lesions. Specific guidance in the current UK management guidelines is somewhat limited, with advice that it would 'seem reasonable' for patients with high-risk SCCs to be closely for observed for recurrent disease for at least two and up to five years, based on 75% of recurrences being detected within two years, and 95% in five years (Rowe et al., 1992, Motley et al., 2002). No recommendations are made regarding low risk lesions. The results of the survey would suggest that most respondents are following this guidance for high-risk lesions, but that there is more division among respondents regarding low-risk lesions. In Australia, where the incidence of skin cancer is so high, the Australian Cancer Network does not make any specific follow-up recommendations for low-risk SCCs, although advises that all patients who have had skin cancer should have an annual skin examination as part of a routine health check. Patients with SCCs treated non-surgically where there is no evidence of histological clearance, and any SCCs considered to be high-risk, are recommended to be closely monitored for up to three years (Australian Cancer Council Australia and Australian Cancer Network, 2008). There have, however, been no studies that have directly

compared regular follow-up by medical practitioners with follow-up by patients themselves.

5.5.2. Identification of research topic and trial scenario

The appraisal of the evidence conducted as part of this thesis showed that the evidence base for the effectiveness of SCC treatments is poor (Chapters 3 and 4). In the absence of evidence from RCTs, this survey has provided useful cross-speciality information about the kind of trials that clinicians would find valuable to guide practice in the treatment of SCC. The results of the survey suggest that there is real enthusiasm among HCPs for research in this area, with nearly half the respondents expressing their provisional expression of willingness to take part in future trial work, either in the form of a full-scale trial or feasibility study, and a further third responding that they may be interested in taking part. However, this is likely to be an overestimate, and willingness to actually recruit patients is will depend upon the actual research question that is taken forward, which at this stage was not known, and the facilities available at their centre. Furthermore, the population who returned the survey are probably those who have an active interest in clinical research which may have biased the results somewhat.

Particular areas of uncertainty identified by the respondents related to optimal excision margins, the role of adjuvant radiotherapy in the management of higher-risk SCCs, and follow-up regimens for SCC patients. There was also interest in the role of newer therapies to treat SCCs, comparison of Mohs surgery with standard excision, and also concern about the lack of a prognostic model on which to base treatment decisions. These topics reflect gaps in the evidence found in the systematic reviews described in chapters 3 and 4, and indicate that there is potential need for well-designed trials in this area.

Development of a scenario for a clinical trial

The results of the clinicians' research priorities were presented to a multidisciplinary group of clinicians, statisticians and a patient representative

from the NCRI non-melanoma subgroup of the Melanoma Clinical Studies Group. Further to the survey and systematic reviews of the effectiveness of existing treatments for SCC (chapters 3 and 4), extensive multi-disciplinary discussions have taken place, through which a trial proposal has evolved. The development of this scenario is discussed in chapters 6 and 9 of this thesis.

5.5.3. Participation in the survey

Advantages of web surveys

Electronic surveys such as the one described in this chapter, have some advantages over mailed surveys in that they are between one third and two thirds less costly to administer (VanDenKerkhof et al., 2004, Raziano et al., 2001), have the potential to be more flexibly designed (Couper, 2001), which subsequently provides more complete responses (Medway and Fulton, 2012, Schleyer and Forrest, 2000), can be administered over a shorter field period (Nguyen and Ho, 2002, Beebe et al., 2007), and as data fields are populated by the respondent there is less opportunity for manual data entry errors (Raziano et al., 2001, VanDenKerkhof et al., 2004).

Potential disadvantages of surveys

Despite the advantages of web-based surveys, it is important to appreciate that they also have some potential drawbacks compared with other types of survey. For example, in the general population response rates may be around 10% lower for web surveys when compared with other modes of survey or mixed modes (Manfreda et al., 2008, Shih and Fan, 2008). Administration of web surveys also assumes access to the internet, a degree of computer literacy in a sample frame that is representative of the population of interest, and compatibility across web browsers to allow successful access, completion and submission of the questionnaire (Nguyen and Ho, 2002, Schleyer and Forrest, 2000).

Improving the reporting of web-based surveys

There have long been calls to improve the quality of reporting of surveys in order to allow the reader to make judgement about the validity of the survey's findings (Cummings et al., 2001, McLeod et al., 2013). Analogous with the CONSORT and STROBE statements for reporting RCTs and observational studies respectively (Schulz et al., Vandenbroucke et al., 2007), a checklist for reporting results of internet e-surveys (CHERRIES) has been compiled with the objective of improving the transparency and quality of web-based surveys (McAlister et al., 2003). The checklist is comprised of 30 items in eight design categories (Table 14). The survey described in this chapter is reported as much as possible according to the checklist, although not all the checklist items are applicable (e.g. view rates of an open website were not applicable as the survey was sent via an e-mail link, and no cut-off was set for time to complete the questionnaire so none had an atypical timestamp).

Healthcare professionals' participation in surveys

Among healthcare professionals, response rates in surveys have shown great variability (Braithwaite et al., 2003), but are typically poor (VanGeest et al., 2007, Cummings et al., 2001), with clinician surveys consistently having lower response rates than non-clinician surveys (Asch et al., 1997) (Cook et al., 2009). As with surveys in the general population, clinician internet-based surveys have lower response rates than those administered by other routes (Raziano et al., 2001, Nguyen and Ho, 2002, VanDenKerkhof et al., 2004), ranging from 11% to 58% (Kim et al., 2001, Cook et al., 2009, Raziano et al., 2001). Furthermore, rates of response appear to have shown a small but significant declining over time (Cummings et al., 2001).

Facilitators and barriers to participation

There are few studies that have examined the facilitators and barriers to clinician participation in surveys and undoubtedly further research into these

areas would provide an evidence base to help inform the most appropriate design for optimal participation in future surveys (Klabunde et al., 2013). Perhaps one of the most significant barriers to clinician participation is lack of time and an increasing number of requests to complete surveys (Kaner et al., 1998, Sudman, 1985). Additional barriers may include the perception that the survey is of low value to the participant, concerns about confidentiality or that the questionnaire items are biased or that a full range of possible responses is not provided (Sudman, 1985). Clinicians may also fear that responses indicating a lack of professional knowledge or practices not meeting best practice standards may reflect negatively either on themselves or on their profession (Klabunde et al., 2013). A Cochrane systematic review of 32 RCTs that evaluated strategies to achieve higher response rates among clinicians for web surveys found that the odds of response were greatest when a 'picture' was included in an e-mail (OR 3.05, 95% confidence intervals 1.84 to 5.06) and when the questionnaire topic was interesting (i.e. questions were particularly relevant to the study participant) (OR 1.85, 95% confidence intervals 1.52 to 2.26)(Edwards et al., 2009). Other strategies that significantly increased the odds of response included non-monetary incentives (e.g. gift cards or lottery participation), having an e-mail that was personalised, and including a submission deadline. However, the odds of response decreased significantly when the word 'survey' was used in the e-mail subject header, and if the e-mail was signed by a male (Edwards et al., 2009).

In this survey, the response rate varied across the professional organisations from 2.4% from the SOeN of the Royal College of Radiologists up to 28% for the BSDS membership, which is in line with the findings of other studies as discussed above. The low rate seen with the SOeN may be a reflection of the survey having been posted on a webpage with access restricted by the Royal College of Radiologists, and would have required members to specifically log on to the site before gaining access to the survey. As the survey was not targeted specifically at clinicians with a particular interest in skin cancer, it is likely that only those with such an interest will have responded, so there will

be an element of self-selection bias. This is reflected in the average number of SCCs treated by the respondents over a 1-year period (Table 16). Interest in the survey subject has already been discussed above as being one of the major incentives for participation in surveys (Edwards et al., 2009). This survey incorporated many of the elements identified by Edwards et al. as increasing the odds of participation, such as personalised e-mails, return deadline, follow-up reminder after initial posting. No monetary or non-monetary incentives were offered to participants in this survey. Monetary incentives have not been shown to significantly increase response rates, although there is evidence that non-monetary incentives do (Edwards et al., 2009). The optimal value of non-monetary incentives is not known though, and for this survey the administration of such an incentive scheme could have proved costly due to the large number of potential participants and impractical to administer.

The aim of this survey was to elicit information about practice and research priorities from a relatively homogeneous group of clinicians who share an interest in the treatment and research of nonmelanoma skin cancer. Therefore the response overall response rates obtained in this survey, which was not specifically targeted at those with an interest in skin cancer, may be considered reasonable and the findings are felt to be valid for the purposes of this research.

Non-response bias

With any survey the question of non-response bias is one which needs to be addressed: is there a systematic difference between those who respond to the survey and those who do not, and is this going to impact upon the external validity of any conclusions drawn from the survey? An element of non-response bias has been suggested by some studies of clinician postal surveys, with reports that women, younger clinicians, non-specialists and recently licensed clinicians are more likely to respond (Barclay et al., 2002,

Cull et al., 2005, Creel et al., 2005). In contrast, a later study of postal survey respondents across specialties found that men were more likely than females to respond, although the level of bias was minimal (McFarlane et al., 2007). Non-response bias has not yet been extensively studied in web surveys (Dykema et al., 2013). However, there is evidence from several studies that higher response rates are not necessarily associated with a lower level of response bias, and even surveys with very high response rates may have significant differences in demographic parameters between responders and non-responders (Barclay et al., 1997, McFarlane et al., 2007). Most studies however, have found no bias or minimal response bias, and it has been suggested that this type of bias is less of a concern for clinician surveys than it is for surveys of the general population as the sample frame is a more homogeneous group and that less than optimal response rates may not necessarily mean that there is excessive bias (Creel et al., 2005, Cull et al., 2005).

5.5.4. Conclusions

This cross-sectional electronic survey has allowed identification of areas of treatment uncertainty which are important to healthcare professionals. Taken together with evidence gaps which were highlighted by the two systematic reviews (Chapters 3 and 4), this has informed the development of four scenarios for a potential RCT. These initial ideas for possible trials are discussed in greater depth in chapter 6, in which the rationale behind them will be described, along with discussion of how a trial proposal evolved through multidisciplinary collaboration.

CHAPTER 6:

EVOLUTION OF A TRIAL

6 EVOLUTION OF A TRIAL

6.1 Introduction

This chapter describes the evolution of the initial ideas for possible clinical trials that emerged from the management uncertainties identified in the survey of healthcare professionals discussed in chapter 5. The survey, together with the results of the systematic reviews (chapters 3 and 4), helped to identify gaps in the evidence and have shaped the development of the trial proposal which will be more fully discussed in chapter 9.

6.2 Initial trial scenarios

Excision margins, the role of adjuvant radiotherapy, optimal follow-up regimens, Mohs compared with standard excision, and the role of newer agents, were the main areas where there were felt to be clinically important uncertainties.

Four trial scenarios were initially formulated and proposed as a starting point for further multidisciplinary discussion and the development of a trial proposal:

1) ***6mm versus 10mm excision margins for SCC classified as T2 by AJCC7 criteria on the basis of being larger than 2cm in diameter but with no other high-risk features***

2) ***6mm versus 10mm excision margins for SCCs defined as T2 tumours according to AJCC7 criteria on the basis of having two or more high-risk features***

3) ***Surgical excision alone with a 6mm margin versus surgical excision plus adjuvant radiotherapy for completely excised high-risk SCCs***

4) ***Surgical excision with 6mm margin versus MMS for high-risk SCCs but located at a low-risk site or at a site without cosmetic or functional considerations where MMS may be preferable.***

High-risk SCCs

All the trial scenarios focussed on high-risk SCCs since these were highlighted in the survey of HCPs as being of a greater priority for research than low-risk SCCs.

Definition of high-risk in these initial scenarios was based on the AJCC7 classification, in which T2 SCCs are defined either as 1) being greater than 2cm in diameter, or 2) of any diameter but which have two or more of the following high-risk features: depth >2mm, poorly differentiated, perineural invasion, Clark level ≥IV (reticular dermis or beyond), or location on the ear or hair-bearing lip.

Excision margins

6mm and 10mm excision margins were chosen based on current management guidelines. UK guidelines of 6mm for high-risk SCCs are based on the results of one study by Brodland and Zitelli in which histological clearance of 95% of SCCs with high-risk features was achieved with a 6mm margin (Brodland and Zitelli, 1992). A more recent study which also used MMS found that margins closer to 5mm and 13mm would be required to clear 95% of low and high risk SCCs respectively (Schell et al., 2013). Recommendations regarding excision margins varies among international guidelines; the US NCCN guidelines advise ' wider surgical margins' than the 4-6mm margin recommended for low-risk SCCs (National Comprehensive Cancer Network, 2013), and the Australian guidelines advocating margins of up to 10mm for SCC greater than 2cm in diameter with even wider margins for very large tumours (Australian Cancer Council Australia and Australian Cancer Network, 2008). There have however, been no prospective RCTs so evidence for the adequacy of narrower versus larger surgical margins is lacking.

Adjuvant radiotherapy

Current UK management guidelines recommend radiotherapy to treat non-resectable tumours with well-defined margins, but do not give any specific recommendation regarding which patients should be considered for adjuvant radiotherapy (Motley et al., 2002), and this was clearly considered to be an area of great clinical importance that was raised in the survey (chapter 5). Australian guidelines advise that patients with any of the following high-risk features should be considered for ART; T4, rapidly-growing, recurrent, close histological margins (<5mm), PNI, lymphovascular invasion, in-transit metastases or regional lymph node involvement (Australian Cancer Council Australia and Australian Cancer Network, 2008). In the United Stated, ART is recommended for any NMSC showing evidence of substantial PNI (involving more than just a few small sensory branches, or a large nerve), of when histological margins are positive after MMS or complete circumferential excision with peripheral and deep margin assessment (National Comprehensive Cancer Network, 2013). However, there have been no RCTs comparing surgery alone to surgery plus ART, and a systematic review conducted by Jambusaria-Pahlajani concluded that current data was insufficient to identify the high-risk features for which ART may be beneficial (Jambusaria-Pahlajani et al., 2009). This was confirmed by the systematic review of observational studies undertaken as part of this thesis and described in chapter 4.

Mohs micrographic surgery

The decision whether to excise cutaneous SCC by MMS or by surgical excision with a pre-defined margin is largely based on the availability of an appropriately trained Mohs surgeon and the facilities to perform the procedure, in addition to the surgeon's personal preference. Despite the perception that there are fewer recurrences after MMS than after surgical excision (Rowe et al., 1992), there have to date been no RCTs to directly compare the techniques for cutaneous SCC, as discussed earlier in this thesis (Chapter 3). In the case of BCCs, there has been an RCT that compared MMS

with surgical excision for primary and recurrent facial BCCs which found no statistically significant difference in recurrence of primary BCC at 5 years (2.5% for MMS versus 4.1% for standard excision, p=0.397), although there was a significant difference for recurrent BCCs (2.4% versus 12.1%, p=0.015)(Mosterd et al., 2008). In the systematic review of observational studies conducted as part of this thesis (chapter 4), there were overall fewer local recurrences after MMS than after surgical excision, although as the confidence intervals overlapped it could not be concluded that the difference was statistically significant. Thus, for primary SCCs there is currently no strong evidence that excision with MMS is superior to surgical excision in terms of recurrences.

Mohs micrographic surgery has the advantage over standard excision in that 100% of the surgical margin is examined and it is more tissue sparing, allowing the surgeon to follow clinically invisible extensions of the tumour to clearance. Current UK management guidelines recommend consideration of MMS for high-risk SCCs especially at difficult sites where wide surgical margins would be difficult to achieve without functional impairment (Motley et al., 2002). In Australia, MMS is recommended for poorly-defined SCCs, those in anatomically sensitive areas, recurrent or residual tumours and for extensive disease (Australian Cancer Council Australia and Australian Cancer Network, 2008). In the United States, the rate of use of MMS in 2009 was 700% greater than it was in 1992 and it is estimated that 1 in 4 skin cancers are excised by MMS (Donaldson and Coldiron, 2012). Recently published appropriate use criteria for MMS from the United States are much more inclusive than the guidelines elsewhere, rating MMS as appropriate for treating SCCs at any body site if they have aggressive features (characterised for the purposes of the paper as ≥2mm deep, Clark level ≥IV, poorly or undifferentiated, perineural/perivascular invasion, sclerosing, basosquamous, small cell, spindle cell, pagetoid, single cell, clear cell, lymphoepithelial, sarcomatoid, infiltrating, or central facial keratoacanthoma). However, the uncertainty of the appropriateness of MMS to treat SCC without aggressive

histological features that were between 1.1 and 2cm in diameter on the trunk and extremities in healthy patients, and up to 1cm in diameter on the trunk and extremities in immunosuppressed patients was highlighted. The only inappropriate indications were for treating SCC with no aggressive features and less than 1cm in diameter, located on the trunk and extremities of healthy individuals (Connolly et al., 2012). The criteria were, however, based largely upon expert opinions rather than high-quality evidence and the indications for MMS remain debateable both in the United States and in Europe (Kelleners-Smeets and Mosterd, 2013).

6.3 Further development of the trial scenarios

The RCT being developed will be the first of its kind to directly address treatment uncertainties for the kinds of primary cutaneous SCC that are commonly seen in clinical practice. Early engagement with professionals who will ultimately be instrumental in delivering the trial that emerges as a result of the research in this thesis is therefore imperative if the trial is to be accepted, funded and ultimately to provide data that will strengthen the evidence-base for SCC treatments and be of benefit to patients in the long-term. Consequently, after initial formulation of the above trial scenarios, there was early liaison with the non-melanoma subgroup of the Skin Cancer Clinical Studies Group of the National Cancer Research Institute (NCRI), which has been central to the development of the trial proposal.

6.3.1. The NCRI Skin Cancer Clinical Studies Group

Established in 2006, the members of this national organisation include dermatologists, plastic surgeons, clinical oncologists, medical oncologists, medical statisticians and a patient representative. The aim of the group is to promote and support high-quality, multicentre clinical trials, translational research and other activities in the field of non-melanoma skin cancer, with particular support for research into rarer NMSCs such as Merkel cell carcinoma, dermatofibrosarcoma protuberans (DFSP) and Kaposi's sarcoma, and for initiatives to improve the evidence base for the treatment of the common keratinocyte tumours such as SCC.

As this research therefore falls into their remit to promote such work, the support from the group has been, and will continue to be, of crucial importance if the trial is to be delivered successfully. Discussions with them have of necessity been detailed and have involved a considerable amount of debate between the members. However, if the dearth of clinical trials in this area is to be redressed, it is important that the trial that is submitted for a funding application has been thought out as carefully as possible in advance. Inevitably there are many issues that need to be addressed when designing a trial like this and it is imperative that all interested stakeholders are on board with the proposal if a funding application is to be successful and the trial is to recruit optimally.

The above scenarios were presented to the NCRI non-melanoma subgroup in January 2012, generating much interest and debate. It was felt that the adequacy of excision was central to the development of future trials, in addition to informing clinical guidelines. However, a trial of excision margins alone would not adequately address important clinical issues around management, such as acquiring a deeper knowledge of the biology of SCC facilitating the development of a prognostic model for making treatment decisions, and the question as to whether ART may be of benefit for particular patients. In order to address such issues, a two-stage factorial design trial was primarily regarded as the best way forward:

		Surgical intervention	
		6mm	**10mm**
ART	**Yes**	✓ 'High-risk' SCC	✓ 'High-risk' SCC
	No	✓ 'High-risk' SCC	✓ 'High-risk' SCC

Participants: Patients with histologically proven high-risk SCCs (definition to be discussed later in this chapter)

Interventions and Comparators:

First stage: Margin-controlled surgical excision, 6mm versus 10mm margin of normal looking skin

Second stage: ART versus normal follow-up

Outcomes:

Primary - loco-regional recurrence, distant metastasis up to 3 years, 5 year survival

Secondary – completeness of excision, quality of life, cosmetic appearance, adverse events.

6.3.2 Factorial randomised controlled trials

There are examples of factorially designed RCTs across many therapeutic areas (Hull et al., 2013, Gridelli et al., 2007, Sever et al., 2001, Emmett et al., 2005). A prime advantage of factorial RCTs is that they allow more than one intervention to be evaluated in the same study, which consequently may be less expensive than running two simultaneous trials, although they are only suitable for interventions that can be used in conjunction with one another as is the case with surgical excision and ART. In addition they can allow for the effects of each intervention to be considered separately and in combination. However, there are some design considerations that need to be taken into account with factorial RCTs. A sample size calculation that is powered to detect the main effects of each intervention makes the assumption that there is no interaction between the interventions, in other words that the effect of receiving the second intervention will remain the same regardless of the treatment arm allocated for the first intervention. However, it is usually difficult to make such a categorical assumption and this may be a particular concern in studies in which the interventions are modifiers of behaviour or

organisations (Montgomery et al., 2003). If investigation of the degree of interaction between the interventions is of importance then a larger sample size would be required in order for the trial to be adequately powered to detect this.

In the case of the trial proposed, it was felt that such a factorial design would be possible given that SCC is a common tumour (although complicated by low-recurrence rates).

Extensive discussions have taken place throughout the development of the trial proposal regarding the definition of 'high-risk' SCC for the purposes of the trial, and also the size of histological margin that will be considered acceptable for classifying an SCC as having been completely excised.

6.3.4 Defining 'high-risk' SCCS

Initially, it was envisaged that AJCC7 criteria would be used to define SCCs at higher risk of recurrence and metastasis and the initial trial scenarios formulated were based on this classification. However, since the publication of the UICC in 2009 and AJCC7 in 2010, there has been criticism of both schemes for the classification of cutaneous SCCs. The AJCC classification and the new BWH criteria that have been proposed as an alternative staging system are discussed in depth in chapter 7 of this thesis. In summary, the BWH classification is based on the number of risk factors present, with subdivision of T2 tumours to allow for better discrimination of those deemed to have a worse prognosis (Table 21).

Table 21: BWH alternative staging system for SCC (Karia et al., 2013)

Primary tumour	Criteria
T0	In situ SCC
T1	0 risk factors
T2a	1 risk factor
T2b	2-3 risk factors
T3	4 risk factors or bone invasion

Risk factors = ≥2cm diameter; poorly differentiated; perineural invasion; invasion beyond subcutaneous fat

Because of the deficiencies of the current AJCC system, the AJCC and BWH criteria will therefore be compared in the analysis of SCCs described in chapter 7. On the basis of these results and on the results in the original publications describing the new BWH staging system (Jambusaria-Pahlajani et al., 2013, Karia et al., 2013), it was decided that the BWH, or a modification thereof, would be more suited for the purposes of the proposed trial, particularly in the identification of the highest-risk tumours which would be eligible for the second randomisation stage to receive ART or no ART.

However, there are some criticisms of the BWH classification. A major drawback of this system is that it does not include depth as a risk factor, as the authors found that this was not recorded in the pathology reports of the tumours they included in their analysis and thus did not feature in their multivariate analysis (Karia et al., 2013). Also, they did not define the percentage of poorly differentiated cells required in order to define the tumour as such. Although PNI was considered to be a risk factor if the nerve involved had a calibre greater or equal to 0.1mm, there was no distinction between intratumoral PNI (i.e. not extending beyond the edge of the SCC on histology) or extratumoral (nerve invasion extending beyond the edge of

surrounding tumour). However, it is believed that extratumoral spread carries a worse prognosis (Miller et al., 2012).

As there is currently no one ideal classification system, the basic structure of the BWH system will be used for the purposes of this trial, but the risk factors upon which T2a and T2b are based will be modified to take into account the core-data set items that are routinely collected in the UK on the RCPath proforma. The differences are summarised in Table 22 .

Table 22: Comparison of BWH high-risk features and modified features for this trial

BWH high-risk features	Modified criteria for trial	Comment
2cm or greater diameter	Greater than 2cm diameter	RCPath dataset item >2cm so modified criteria would make data easier to capture
Depth not a factor	Greater than 4mm deep	RCPath dataset item >4mm
Poorly differentiated	Poorly/undifferentiated	Based on most poorly differentiated region irrespective of % present
Perineural invasion in nerve calibre ≥0.1mm	Perineural invasion	Nerve calibre not recorded in dataset.
Invasion beyond subcutaneous fat	Invasion beyond subcutaneous fat	Recorded in RCPath dataset
Site not a feature	Ear or lip location	Site not a feature of BWH but ear or lip location are a high-risk feature in AJCC7

6.3.5 Histological margins

In the proposed trial only SCCs that have been adequately excised in the first surgical stage will be eligible to be randomised in the second if they meet the other eligibility criteria for the ART stage (i.e. T2b tumours). What constitutes an adequate histological margin is very debateable and re-treatment based on the size of histological margins is inconsistent among clinicians. In the Brodland and Zitelli study upon which current clinical excision margins recommendations are largely based (Brodland and Zitelli, 1992), histological

clearance was set at greater than one microscopic high power field (0.5mm), and this has also been used in one other study as the cut-off for adequacy of excision (Thomas et al., 2003). However, a recent study reported that of 79 SCCs that were re-excised due to involved or close histological margins (<1mm), 11% recurred (9 of 79). Twenty-one of the re-excised SCCs had residual tumour on re-excision, with recurrence in six (29%) of these, compared with 5% recurrence in the 58 SCCs in which no residual tumour was found (Bovill and Banwell, 2012). However, an unexpected finding in this study was that 2 of 16 'closely' excised SCCs (13%) had residual tumour on re-excision, although numbers were small. On the basis of their findings the authors recommended re-excision of any SCCs where narrow or close margins were reported on histology. Nevertheless the evidence base regarding the adequacy of histological margins is very limited.

The UK clinical guidelines (Motley et al., 2002) assume that an SCC has been incompletely excised if tumour cells extend to the margin. The RCPath requires a mandatory core minimum reporting of lateral and deep margins of: a) margin involvement (0mm); b) margins clear but close (less than 1mm); c) margins clear (1mm to 5mm); or d) margins clear (>5mm) (Chaudhuri et al., 2006). It is the SCCs that fall into the 'clear but close category' (i.e. closer than 1mm) that are most controversial, and although one-third of regional dermatologists considered SCCs reported as such to have involved margins, there was no consistent approach to the re-excision of these SCCs (Chaudhuri et al., 2006). This is undoubtedly an area where the evidence needs to be strengthened in order to inform future guidance. Therefore, for the purposes of this study and based on the data that is collected on the RCPath proforma, only SCCs with peripheral and deep margins greater than 1mm will be eligible for the second randomisation stage. However, one of the secondary outcomes will be completeness of excision determined by histological margin measurement following surgical excision, so this data which will add to the evidence base regarding the adequacy of histological margins.

6.4 Summary

As a result of the clinically important treatment uncertainties that were identified by healthcare professionals, four initial trial scenarios were drawn up which were presented to the NCRI non-melanoma CSG with a view to further development of a proposal for an RCT for submission for funding. The next two chapters in this thesis describe feasibility work which was undertaken in order to assess the likely numbers of patients and the types of SCC that would be potentially be eligible for recruitment into the RCT being developed, and to assess the acceptability of such a trial and possible barriers to recruitment which would need to be considered when designing the trial.

CHAPTER 7:

CASE SERIES OF SQUAMOUS CELL CARCINOMAS TREATED IN NOTTINGHAM

7 CASE SERIES OF SQUAMOUS CELL CARCINOMAS TREATED IN NOTTINGHAM

7.1 Abstract

Introduction

There is currently no consistent prognostic model for cutaneous SCCs and further elucidation of the inter-relationship between the various prognostic features and outcomes will require large prospective studies to be conducted. The main objective of this part of the research was to determine the types and numbers of SCC that are treated over the course of a year at a large regional centre. This information will guide the design of a randomised controlled trial (RCT) which will provide data that should help clinicians to target particular SCCs treatments appropriately and more consistently than is currently the case.

Methods

Using a specially designed database, data were collected on all cutaneous SCCs submitted to the histopathology department for two 12-month periods, 2006-7 and 2010-11. Information was gathered on demographics, prognostic features, and for the 2006-7 dataset information was also collected on the occurrence of adverse outcomes within 5 years of treatment. The two datasets were compared for demographic distribution and numbers treated. An analysis of the specialties treating SCC was also done for the 2010-11 dataset. SCCs were classified according to AJCC criteria, and also according to an alternative staging system, the Brigham and Women's Hospital scheme, which will be utilised to identify high-risk SCC eligible for entry into the proposed RCT. The number of patients that would be eligible for each stage of randomisation in the proposed trial was approximated based on the percentages of SCCs classified in each T-stage.

Results

The number of patients with SCC treated in Nottingham increased from 357 in 2006-7 to 423 in 2010-11, and there was also a significant increase in the age of treated patients from 76 years to 78 years (independent sample t-test p=0.04) . The majority of SCCs were treated by dermatologists and plastic surgeons, with women and larger SCCs being more likely to be treated by plastic surgeons.

Mean clinical excision margins were slightly above the 4mm for low-risk and 6-mm for high-risk margins, as recommended in current UK guidelines. There was histological involvement of the surgical edge in 3% of excised SCCs, with the deep edge being significantly more likely to be implicated than the peripheral edge (p=<0.001).

Adverse outcomes within 5 years as a result of SCC were rare, with overall local recurrence of 6.2%, regional recurrence of 3.3% and SCC-attributable death of 1.5%. There were no distant metastases recorded in this dataset. On multivariate analysis, local recurrence was associated with PNI and vascular invasion, and regional recurrence with diameter of >2cm. Only increased age was found to be significantly associated with SCC-related death.

Just over 50% of SCCs that were classifiable from the data available were T2 tumours by both the most recent AJCC7 classification scheme, and by the alternative BWH scheme. However, BWH staging allows for an additional T2b substage to better stratify outcomes dependent on the number of risk factors present. Based on this scheme, 19% of all BWH classifiable tumours would be classed as T2b, and potentially eligible for randomisation into the second adjuvant radiotherapy (ART) stage of the proposed RCT. Inclusion of >4mm depth as an additional risk factor would increase the number of T2b SCCs to 30.5% of all BWH classifiable tumours.

Conclusion

SCC is a common tumour and large numbers are treated annually in this regional centre. This study has allowed estimation of the types and numbers of SCCs in order to give an approximation of the number of patients who could potentially be eligible to be recruited into the proposed trial based on the prognostic features associated with their SCC and its classification.

7.2 Introduction

This chapter describes work that has been done to gain an overview of the numbers, types, and baseline 5 year outcomes of SCCs treated across specialties at a regional centre each year, in order to assess likely numbers and demographics of patients potentially eligible for recruitment into the proposed RCT being developed and to guide sample size calculation for the proposed trial. The evolution of the proposed trial has been discussed in chapter 6 and the current trial proposal will be described in greater detail in chapter 8; briefly it will involve two randomisation stages, the first to compare outcomes between surgical excision with wide margins and Mohs micrographic surgery, and the second stage to evaluate the effect of adjuvant radiotherapy versus no adjuvant radiotherapy. SCCs have been assessed in terms of the presence of various prognostic features and classified according to both the most recent AJCC classification (Edge and Compton, 2010) and also an alternative SCC staging scheme, the Brigham and Women's Hospital scheme (BWH)(Karia et al., 2013), which aims to better discriminate SCCs in terms of their prognosis.

7.2.1. Tumour classification of SCC

The Tumour Node Metastasis (TNM) system was originally developed and is maintained by the Union for International Cancer Control (UICC) in an attempt to achieve consensus on one globally recognised standard for classifying the extent of spread of cancer (Sobin et al., 2009). The TNM system is also used by the American Joint Committee on Cancer (AJCC) (Edge and Compton, 2010) for staging cancer, but unlike the UICC, the AJCC classifies SCCs separately from other skin tumours and in the most recent edition (AJCC7) has attempted to better discriminate tumours at higher risk of recurrence based on the presence of particular features. Comparison of the UICC, and the AJCC 6th and 7th editions is made in Table 23. Although a considerable improvement on the AJCC6 criteria, neither the UICC nor AJCC

classification has been deemed suitable for a realistic estimate of the risk of metastasis of SCC (Breuninger et al., 2012). For the UICC classification in which the cut-off between T1 and T2 tumours is solely maximum diameter of greater than 2cm (Sobin et al., 2009), most poor outcomes occur in T1 tumours as this group contains many tumours with risk factors other than diameter, whereas in the AJCC7 system, the bulk of poor outcomes occur in T2 SCCs (Karia et al., 2013). The AJCC criteria have also been criticised for their omission of particular features that are associated with increased risk, such as occurrence of SCC in a chronic burn, scar or area of inflammation, recurrent disease and immunosuppression in the host (Buethe et al., 2011a). The authors of the AJCC7 criteria concede that their staging scheme is not perfect and that further multivariate analyses are still required to determine the relative contributions of the individual risk factors towards prognosis and to inform the development of treatment algorithms (Farasat et al., 2011).

Table 23: Comparison of the UICC, AJCC6 and AJCC7 staging schemes

	UICC (Sobin et al., 2009)	AJCC6 (Greene et al., 2002)	AJCC7 (Edge and Compton, 2010)
T1	≤2cm in greatest dimension	≤2cm in greatest dimension	≤2cm in greatest dimension but with fewer than 2 high-risk features*
T2	>2cm in greatest dimension	>2cm up to <5cm in greatest dimension	>2cm with fewer than 2 high-risk features* OR Tumour any size with ≥2 high-risk features*
T3	Invasion of deep structures e.g. muscle, bone, cartilage, jaws, orbit	>5cm in greatest dimension	Invasion of mandible, maxilla, orbit, temporal bone
T4	Direct or perineural invasion of skull base or axial skeleton	Invasion of deep extradermal structures	Invasion of the skeleton (axial or appendicular) or PNI of the skull base

* >2mm thick; Clark level ≥IV; perineural invasion; primary site ear or no-hair-bearing lip; poorly or undifferentiated

Alternative staging systems have been proposed since the publication of the AJCC7 criteria and the rationale underpinning them will need consideration when the AJCC criteria are updated for the eighth edition which is due in 2017 (https://cancerstaging.org/About/news/Pages/8th-Edition-Publication-Date-Announced.aspx). A simplified T staging system has been proposed by Breuninger (Breuninger et al., 2012) in an attempt to estimate risk of metastasis based initially on diameter (clinical T - ≤2cm = 'low' risk; >2cm = 'high' risk), with further subdivision into 'no risk', 'low risk' and 'high risk' post-operatively based on the depth of invasion (≤2mm, >2-6mm, and >6mm respectively). Desmoplastic and undifferentiated tumours, ear location and immunosuppression are considered as co-risk factors for metastasis in this proposed scheme. However, the presence of PNI is not included as a co-risk factor as the authors considered this feature only to be exhibited by desmoplastic SCCs (Breuninger et al., 1997), which were in their own multivariate analysis significantly associated with local recurrences, with or without PNI (Brantsch et al., 2008). However, as discussed above, other studies have suggested that PNI is an important risk factor for poorer prognosis, and none of the SCCs reported as having PNI in this study were associated with desmoplastic pathology. As the presence of PNI is one of the major factors upon which an MDT decision to administer ART is currently made, albeit on a poor evidence base as discussed in chapter 4, it would be difficult to reconcile using a staging system in the proposed trial which does not take the presence of PNI into account.

A further alternative staging system has been recently proposed, which although still based on the AJCC7 staging, appears to offer improved prognostic discrimination (Jambusaria-Pahlajani et al., 2013, Karia et al., 2013). The AJCC7 T2 stage is very heterogeneous and patients who do well are clustered with those whose prognosis is poor, with 69% of all local recurrences, 83% of regional metastases, and 92% of SCC attributable deaths reported in the 91 SCCs (44% of a total of 207) that were categorised as T2 according to AJCC7 criteria (Jambusaria-Pahlajani et al., 2013). The alternative

system attempts to improve the homogeneity (outcomes are similar within staging groups), monotonicity (outcomes worsen with increasing stage) and distinctiveness (outcomes differ between staging groups), based on four risk factors that were identified by the authors' own multivariate analysis (Table 24).

Table 24: Alternative SCC staging scheme (Karia et al 2013)

BWH Stage	Criteria
T0	In situ SCC
T1	No risk factors
T2a	1 risk factor
T2b	2-3 risk factors
T3	4 risk factors OR bone invasion
* tumour diameter ≥ 2cm; poorly differentiated histology: PNI in nerve of calibre ≥0.1mm; invasion beyond subcutaneous fat	

The larger of the two studies (Karia et al., 2013) which included 1817 SCCs, reported that although the higher T2b and T3 stages contained only 5% of SCCs in the total cohort, they accounted for the 60% of poor outcomes, including 70% of regional metastases. Although these findings require refinement and validation, they suggested that the alternative scheme could be used upon which to base further studies of sentinel lymph node biopsy (SNLB) and adjuvant radiotherapy. A recent evaluation of the association between positive sentinel lymph node biopsy and stage, concluded that there appeared to be better stratification of outcomes in the alternative staging system compared with the AJCC7 staging system, with positive SNLBs in none of the 9 BWH T1 tumours, 6 of 85 (7%) T2a SCCs, 5 of 17 (29%) T2b SCCs, and in 3 of 6 (50%) of T3 SCCs (p=0.02) (Schmitt et al., 2014).

In the proposed trial which will be discussed in greater depth in chapter 8, the second stage will involve randomisation to receive ART or no ART. However,

only SCCs that are considered to be particularly high-risk will be eligible for this stage, as it is in this group where there is greatest uncertainty as to the effectiveness of ART, which was borne out in the survey of healthcare professionals described in chapter 5 of this thesis. Also, as there are potential long-term adverse effects of administering radiotherapy, it would ethically be unacceptable to subject patients to the procedure if their tumour is lower-risk and the prognosis with surgery alone is relatively good. As the BWH scheme does appear to give better stratification of prognosis for patients than that of AJCC7, a modification of this scheme will be used in the proposed trial to identify those patients with higher-risk SCC, and in whom it is important to investigate whether ART has an important role or not. This chapter therefore includes a comparison of the AJCC7 and BWH classification schemes, the number of SCCs according to stage and an analysis of outcomes for each scheme. However, the BWH scheme has been adapted slightly in accordance with data that is collected routinely in the RCPath dataset (Chaudhuri et al., 2006) in order to reflect more accurately what would happen in the actual trial. Therefore, the BWH risk factor of 'tumour diameter of 2cm or more' is modified to 'greater than 2cm', and instead of PNI in a 'nerve calibre of equal to or greater than 0.1mm' any PNI will be considered to be a risk factor. Invasion 'beyond subcutaneous fat' is modified to 'subcutaneous or beyond' as a compromise between the BWH and AJCC7 classification, in which invasion at or beyond the reticular dermis is a risk factor. One of the major criticisms of the BWH scheme is that it has not taken into account the Breslow thickness of the tumour, as this was not routinely reported on their pathology reports (Jambusaria-Pahlajani et al., 2013). However, depth above 4mm has been shown to be an important independent risk factor for metastasis in several studies (Kraus et al., 1998a, Dinehart and Pollack, 1989, Breuninger et al., 1997, Brantsch et al., 2008), and is one of the RCPath's high-risk features (rather than >2mm which is incorporated into the AJCC7 classification as a risk factor). Therefore, in order to better estimate likely numbers of SCC that would be eligible in the proposed trial, those that are deeper than 4mm are included in a separate analysis.

7.3 Methods

7.3.1. Data collection

An anonymised web-based Access database was created to collect retrospective data on SCCs submitted to the Histopathology Department at Queen's Medical Centre, Nottingham. There were two data collection periods: the first was conducted between 1 April 2011 and 31 March 2012 with the purpose of giving a rapid overview of the number of SCCs treated annually in Nottingham, and by which specialty, and the second was between 1 April 2006 and 31 March 2007, data from which was analysed in greater depth in terms of prognostic features and outcomes within five years after treatment. Primary cutaneous SCCs were identified by the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT codes) M80703, 80713, 80743, 80753 and 80513 and histopathology data from the dataset recorded in the appropriate fields.

Features of the tumour including anatomic location, diameter, depth of invasion, Clark level, differentiation, histological growth pattern, perineural invasion and vascular invasion were recorded. In addition, for the 2006-7 database from which outcome data was to be assessed, excised tumours were classified according to T classification based upon the sixth and seventh editions of the American Joint Committee on Cancer (AJCC) staging criteria (Edge and Compton, 2010) and the BWH criteria (Karia et al., 2013). T classification in the sixth edition was based upon tumour diameter and did not take into account additional high risk pathological features (T1 =<2cm, T2=2-5cm, T3 >5cm), whereas in the seventh edition, T2 SCCs are those with either a diameter of greater than 2cm, or those equal to or less than 2cm in diameter, but which also have 2 or more additional high risk features (>2mm deep, Clark level IV or beyond, the presence of perineural invasion, being located on the ear or non-hair-bearing lip, or being poorly differentiated or undifferentiated). BWH T classification was based upon the presence of the

number of high-risk features present (≥2cm diameter, poorly differentiated, PNI, invasion into subcutaneous fat or beyond). As data on depth and level of invasion was only routinely available for excised SCCs, only these samples were given a T classification. Treatment of tumour and clearance of lateral and deep surgical margins was recorded when possible. Non-invasive SCCs, actinic keratosis, Bowen's disease and recurrent SCCs were not included in the analysis. Tumours were excluded if they were in ano-genital locations or mucosal.

SCCs identified from the earlier dataset were linked to the clinical record database via hospital identification numbers and data on recurrences (local or to regional lymph nodes), distant metastases, and death, either attributable to SCC or from another cause, which occurred within five years of treatment were recorded on the research database by the Dermatology Department. Deaths that were recorded as attributable to SCC were checked by the Dermatologist from the patient's case records. For patients with more than one SCC treated over the course of the year, the SCC with the greatest number of adverse prognostic features was selected for analysis of potential trial participant numbers.

7.3.2. Statistical analysis

Baseline demographic variables and clinical and histopathological data were analysed using descriptive statistics and frequency tabulation in SPSS 21. Statistical significance of differences between variables was assessed by chi-squared test or, in the case of small frequencies, by Fisher's test. Differences between means of continuous variable were assessed with independent samples T-test. Levene's test was used to test for equality of variances. P values of ≤0.05 were considered to be statistically significant. Outcome frequencies were based upon excised tumours which had data recorded for local recurrence, regional recurrence, distant metastases, and death.

The simultaneous impact of different risk factors was determined by multivariable analysis using a logistic regression model on the full data set.

Patients with missing exposure data were coded as 'missing' and included in the analyses. Collinearity between variables was assessed using chi-squared, Fisher's Exact or t-tests, as appropriate. The regression models were built using the variables identified as significantly related to the outcome in univariable analyses. The models were then augmented through deleting variables that became non-significant. Finally, variables which were not significantly related to the outcome in the univariable analyses were added individually to assess whether they became significant in the multivariable model. The final multivariable models included variables which were statistically associated with the outcome at the 5% level. Results from the logistic regression analyses are reported as odds ratios with 95% confidence intervals.

7.3.3. Approval

Written permission to conduct the study was obtained from the Cancer and Associated Specialties Directorate Clinical Director of Nottingham University Hospitals NHS Trust.

7.4 Results

7.4.1. Comparison of the 2006-7 and 2010-11 datasets

There were 518 primary invasive cutaneous SCCs identified through the initial pathology database search of specimens submitted between 1 April 2010 and 31 March 2011. Six were excluded as they were ano-genital or located at non-cutaneous sites, leaving 512 specimens in 423 patients. The initial pathology database search for April 2006 to March 2007 identified 431 primary invasive SCCs that had been submitted over the 12 month period. Ten of these were excluded upon further review as they were sited in ano-genital, mucosal or non-cutaneous locations, so in total there were 421 SCCs from 357 patients. During the 2010-11 period, there were 91 more SCCs in 66 more patients compared with the 2006-7 data, representing a 22% increase in SCCs submitted, and an 18.5% increase in the number of patients treated.

Demographics

The demographics of the patients in each of the databases are compared in Table 25. The male: female ratio was 1:0.54 in 2006-7 and 1:0.61 in 2010-11, which was not significantly different between the two datasets (p=0.51).

Table 25: Comparison of patient characteristics in 2006-7 and 2010-11 datasets

Characteristic		Number (%) of patients		p-value χ^2/independent sample t-test
		2006-7 (N=357)	2010-11 (N=423)	
Gender	**Male**	231 (64.7)	263 (62.2)	0.51
	Female	126 (35.3)	160 (37.8)	
Age		Mean 76.0 years (range 34–99 years)	Mean 77.7 years (range 15-101 years)	**0.04**

An independent samples t-test revealed that patients treated during 2010-11 were significantly older than those treated during 2006-7 (mean difference =-1.68, 95% CI -3.28 to -0.078, p=0.04). There was no statistically significant difference between the mean ages of males and females in the study population for either of the datasets (independent samples t-test, p=0.416 and p=0.422 for 2006-7 and 2010-11 respectively).

Between 2006-7 and 2010-2011 there were no statistically significant changes in the distribution of patients according to age group categories (chi-squared test, p=0.46) (Table 26). However, there may have been a slight increase in the number of proportion of patients over 80 years between 2006-7 and 2010-11, although it is not possible to confirm the significance of this from the data available.

Table 26: Number of patients in each age group category for the two datasets

Age category (years)	Number (%) of patients	
	2006-7 (n=357)	2010-2011 (n=423)
<40	4 (1.1)	2 (1.1)
40-49	4 (1.1)	4 (1.0)
50-59	24 (6.7)	23 (5.4)
60-69	55 (15.4)	57 (13.5)
70-79	113 (31.6)	125 (29.6)
>80	157 (44.0)	212 (50.1)

The majority of patients had one SCC excised during each of the 12-month periods (96% for 2006-7 and 94% for 2010-11). During 2006-7, ten (3%) patients had a second SCC submitted for histopathology, and four patients (1%) had three. For the 2010-11 12 month period, there were 20 patients (5%) with a second SCC, three (0.7%) with four SCCs, and one (0.2%) for whom six separate SCC were submitted (a patient with xeroderma pigmentosum).

Specimen types

The types of specimens submitted during each of the two data collection periods is summarised in Table 27.

Table 27: Comparison of specimen types submitted during 2006-7 and 2010-11

Specimen type	Number of specimens (%)	
	2006-7 (N=421)	2010-11 (N=512)
Excision	298 (70.8)	356 (69.5)
Incisional biopsy	5 (1.2)	3 (0.6)
Punch biopsy	61 (14.5)	83 (16.2)
Shavings	3 (0.7)	9 (1.8)
Curettings	34 (8.1)	25 (4.9)
Widening of previous excision	5 (1.2)	14 (2.7)
Not specified	15 (3.6)	22 (4.2)

The types of specimens submitted to histopathology did not appear to vary significantly between 2006-7 and 2010-11 (chi-squared test, p=0.117).

7.4.2. Specialties treating cutaneous SCCs

The 2010-11 database was analysed according to treating specialities (Figure 46).

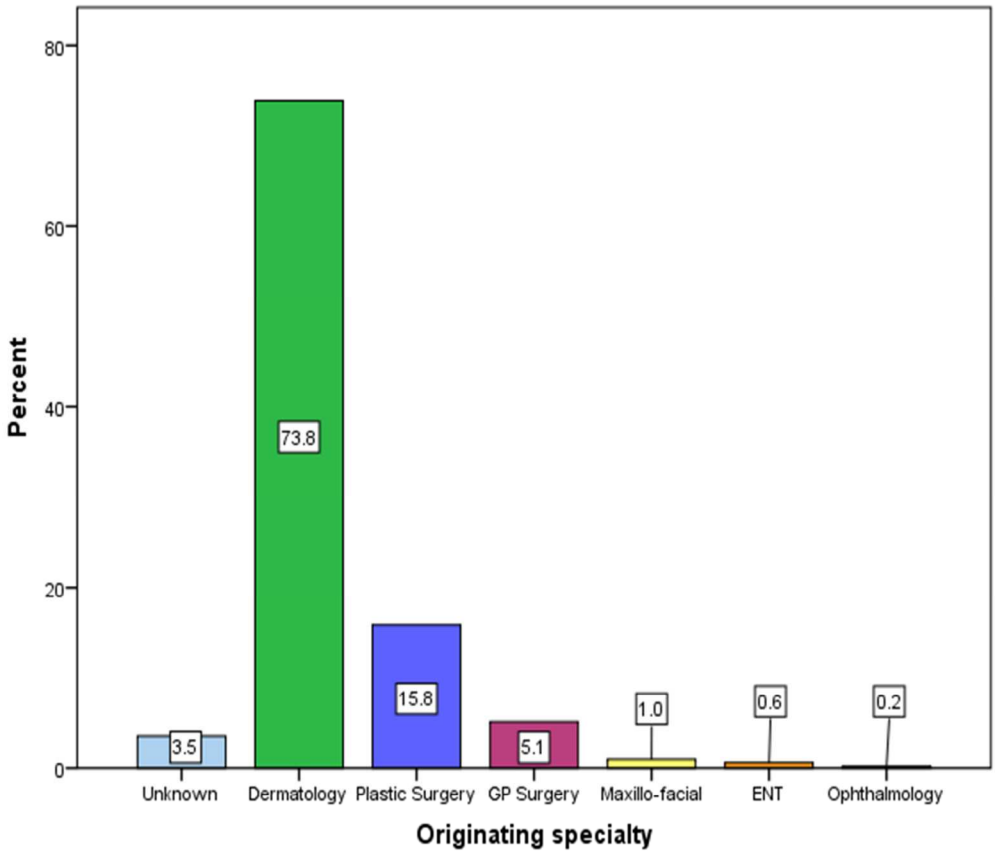


Figure 46: Specialties treating cutaneous SCCs (2010-11)

90% (459/512) of SCCs submitted to histopathology were sent by dermatologists (74%) or plastic surgeons (16%). 5% (26) were sent from GPs, of which 6 were punch biopsies, 4 were curettings, 1 was an incisional biopsy, and 1 was not specified. One of the punch biopsies from an SCC located on the scalp was followed with excision by the GP. The remaining SCCs were sent from maxilla-facial surgeons (5/512), ENT surgeons (3/512) and ophthalmological surgeons (1/512).

7.4.3. Comparison of SCCs treated by dermatologists and plastic surgeons

Excised SCCs submitted by dermatologists and plastic surgeons were analysed to see if there were any differences between the types of SCCs that are treated by these specialties (Table 28).

Table 28: Comparison of SCCs excised by dermatologists and plastic surgeons (2010-2011 dataset)

	Dermatology	Plastic Surgery	p-value
Gender: **Male** **Female**	**65.2% (133/204)** **34.8% (71/204)**	**48.1% (25/52)** **51.9% (27/52)**	**0.023**
Mean age (SD)	77.6 (10.4)	76.9 (13.0)	0.692
Mean diameter [mm] (SD)	**12.1 (7.2)**	**18.8 (13.5)**	**<0.001**
Mean depth [mm] (SD)	3.4 (2.1)	4.2 (4.5)	0.124
Invasion subcutaneous or beyond	20.0% (48/240)	29.2% (19/65)	0.111
Poorly differentiated	25.9% (64/247)	33.3% (22/66)	0.230
PNI present	4.1% (10/241)	1.5% (1/65)	0.316
Mean histological peripheral margin [mm] (SD)	5.1 (2.0)	5.4 (3.1)	0.436
Mean histological deep margin [mm] (SD)	3.5 (2.3)	3.7 (3.2)	0.640

Plastic surgeons excised SCCs from more females than males during the 12 month period analysed; this was a reversal of the male: female ratio of 1: 0.6 across the entire database and was also significantly different from the

proportion of males to females treated by dermatologists during the same time period (chi-squared test, p=0.023). Plastic surgeons were also treating SCCs that were significantly larger in diameter than their dermatology colleagues (mean diameter 18mm for plastic surgeons compared with 12mm for dermatologists; (t-test, p<0.001). There were no significant differences found in the other variables assessed.

7.4.4. Characteristics of tumours

As outcome data was only available for the 2006-7 dataset, these tumours were analysed for their characteristics and staged according to the AJCC6 , AJCC7, BWH criteria and RCPath features.

375 unique SCCs were included in the analysis. There were no significant differences between the demographics of patients who had excision and those for whom another type of specimen was submitted but in whom there was no matching excision specimen (male: female 66.7%:33.3% for excisions versus 61.7%:38.3% for others [chi-squared test, p=0.407]; mean age 76.0 years (SD11.89) versus 75.6 years (SD 10.19)[independent samples t-test, p=0.780]).

Tumour characteristics are summarised in Table 29.

Characteristic		Number (%) of tumours (N=375)
Location	Head and neck	231 (61.6)
	Trunk	23 (6.1)
	Upper limb	53 (14.1)
	Lower limb	63 (16.8)
	Not specified	5 (1.3)
Tumour diameter	Mean	18.1 mm
	Median	12.0 mm
	=<2 cm	162 (43.2)
	>2 cm	33 (8.8)
	Not specified	180 (48.0)
Tumour depth	Mean	4.9 mm
	Median	3.0 mm
	=<2 mm	90 (24.0)
	2.1-<=4 mm	124 (33.1)
	>4 mm	64 (17.1)
	Not specified	97 (25.8)
Level of invasion	Papillary dermis	5 (1.3)
	Upper reticular dermis	14 (3.7)
	Mid reticular dermis	87 (23.2)
	Deep reticular dermis	113 (30.1)
	Subcutaneous	54 (14.4)
	Not specified	102 (27.2)
Differentiation	Well/moderately	212 (56.5)
	Poor/undifferentiated	88 (23.5)
	Not specified	75 (20)
Histological type	Classic/no special type	245 (65.3)

	Acantholytic	7 (1.9)
	Spindle cell	1 (0.3)
	Desmoplastic	3 (0.8)
	Not specified	119 (31.7)
Perineural invasion	Present	16 (4.3)
	Not present	268 (71.5)
	Not specified	91 (24.3)
Vascular invasion	Present	6 (1.6)
	Not present	278 (74.1)
	Not specified	91 (24.3)

Table 29: Characteristics of SCC treated 2006-7

Anatomical location

There were significant differences in the anatomical location of SCCs between men and women (chi-squared test, $p<0.0001$) (Figure 47), where it appeared that men were more likely to have an SCC located in the head and neck region, and women to have and SCC on the lower limbs. In the head and nick region, there was also a statistically significant difference between men and women in the distribution of their SCCs (chi-squared test, $p<0.0001$), with men more likely to have an SCC in the ear area ($p<0.0001$), whereas women were more likely to have them on the cheek ($p=0.04$), lip ($p=0.05$) or neck ($p=0.03$). Although a greater percentage of SCCs in males were located on the scalp (21.2% versus 9.6% in females), this did not quite achieve statistical significance ($p=0.0687$)(Figure 48).

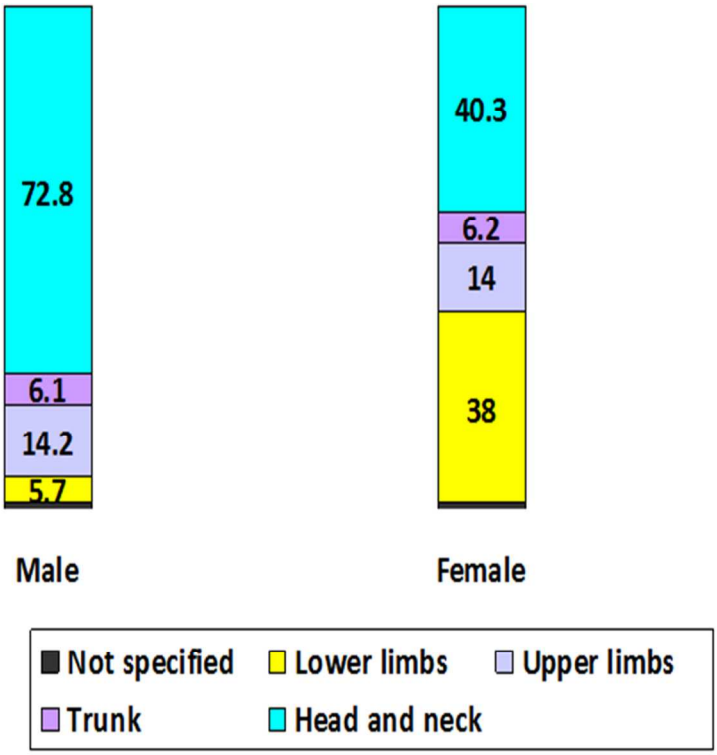


Figure 47: Anatomical distribution of SCCs in males and females (%)

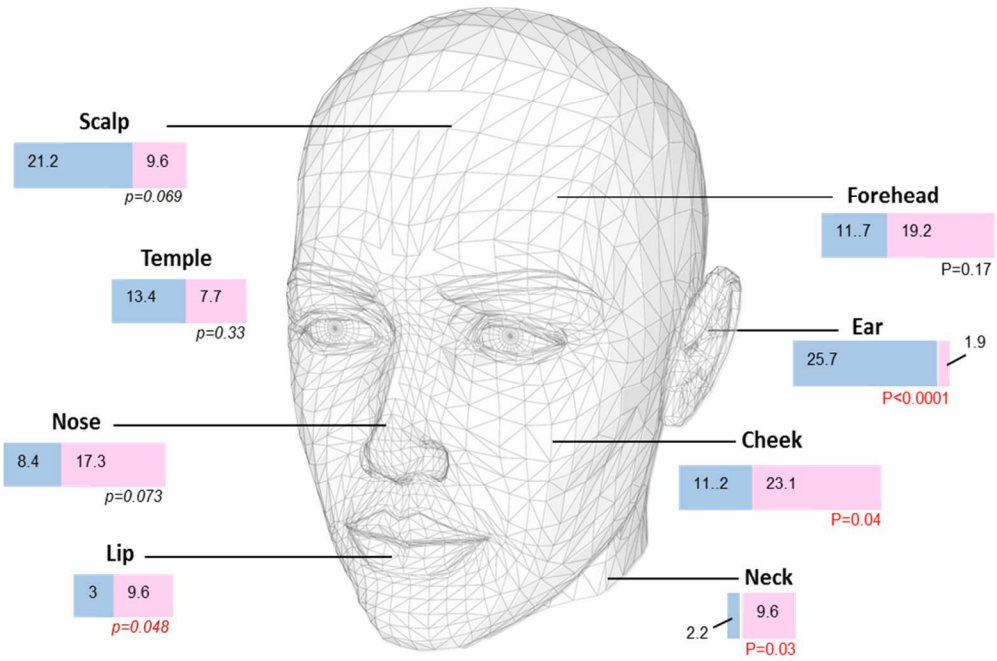


Figure 48: Distribution of head and neck SCC (%) by gender

7.4.5. Treatment Modality

Treatment modality was not usually recorded on the histopathology database (362/421 [86%]). Excisional surgery was recorded as the treatment modality for 57/421(13.5%) of SCCs and Mohs surgery in 2/421 (0.5%).

7.4.6. Clinical excision margin

During 2006-7, clinical excision margins were only recorded for 7 of the 298 excisions (2.3%), ranging from 2mm to 10mm (mean 5mm). Recording of excision margins was much more complete during 2010-11, with a mean clinical excision margin of 5.2mm in the 126 of 352 (35.7%) excisions for which this data was available. These ranged from 1.7mm for a 0.9mm diameter SCC on the arm to 50mm for a 30mm diameter SCC on the thigh. The mean clinical excision margin for SCCs that were 2cm or less in diameter was 4.5mm (n=97), whereas for SCCs greater than 2cm in diameter it was 7.8mm (n=21).

There was a trend towards taking smaller excision margins for SCC located on the head or neck compared with those elsewhere on the body (mean excision margins 4.4mm (n=78) and 6.3mm (n=48) respectively), although statistical significance was not quite reached (independent t-test p=0.072).

7.4.7. Peripheral and deep histological margins

During 2006-7, distance of tumour from the peripheral and deep margins was recorded in 213 excised SCCs. The mean peripheral histological margin was 5.17mm (range 0 to 28mm) and the mean deep histological margin was 3.52mm (range 0 to 23mm). In 2010-11, distance of tumour to the peripheral margin was recorded for 301 excisions, and the distance to the deep margin in 296 excisions. During this time period, the mean peripheral histological margin was 5.06mm (range 0 to 15mm) and the mean deep margin was 3.5mm (range 0 to 19mm).

The smallest distances from the edge of tumour to the peripheral and deep edges of excision specimens were categorised according to the RCPath minimal dataset proforma for SCCs, and summarised in Table 30.

Table 30: Histological peripheral and deep margins; proportions of excised SCCs according to RCPath criteria (2006-7 and 2010-11)

Distance from tumour edge to specimen edge (mm)	Number of excisions (%): Peripheral		Number of excisions (%): Deep	
	2006-7 (N=213)	2010-11 (N=301)	2006-7 (N=213)	2010-11 (N=296)
0 (transecting)	4 (1.9)	2 (0.7)	6 (2.8)	8 (2.7)
0.1 to 0.9 (close but clear)	2 (0.9)	3 (1.0)	21 (9.9)	17 (5.7)
1 to 5mm (clear)	119 (55.9)	180 (59.8)	142 (66.7)	216 (73)
>5mm (clear)	88 (41.3)	116 (38.5)	44 (20.7)	55 (18.6)

In total there were 7 of 213 SCCs (3.3%) in which the peripheral or deep margins were transected during 2006-7.

Three SCCs transected both peripheral and deep margins:

1) A 1mm diameter well-differentiated SCC on the neck, 4mm deep and extending to the mid- reticular dermis
2) An 11mm diameter moderately differentiated SCC on the ear, 3mm deep and extending to deep reticular dermis
3) A 20mm moderately differentiated, acantholytic SCC on the cheek, 10mm deep and extending to deep reticular dermis.

Narrow or transecting peripheral histological margins (less than 1mm) were found in 6/213 (2.8%) of excisions for which this data was available,

compared with narrow or transecting deep histological margins in 27/213 (12.7%) of excised SCCs. Deep margins were more likely to be involved (transected or close but clear margin) than peripheral margins, a difference which was statistically significant (Fisher's test $p<0.001$).

Three SCCs, two on the ear and one on the scalp, transected deep margins but had clear peripheral margins (1mm or greater), 21 had close but clear deep margin but clear peripheral margins, and one ear SCC had a close peripheral margin but clear deep margin.

During 2010-11, transecting peripheral or deep margins were recorded in 9 of 301 SCCs (3.0%). One poorly differentiated 25mm diameter SCC located on the ear transected both peripheral and deep margins. Seven of 296 SCCs (2.3%) transected the deep margin but had clear peripheral margins of more than 1mm, whereas one 12mm diameter SCC located on the breast transected the peripheral margin although the deep margin was clear. Narrow or transecting peripheral margins were recorded in 5/301(1.7%) of excised SCCs, and narrow or transecting deep margins in 25/296 (8.4%) SCCs, which again was a statistically significant difference (Fisher's test $p<0.001$).

7.4.8. Tumour classification based upon AJCC staging criteria

Comparison between the sixth and seventh editions of the AJCC T classifications is summarised in Table 31. The number of SCCs that would be classified as T2 is upgraded when compared with the earlier sixth edition , based upon diameter greater than 2cm, or having a diameter less than 2cm with two or more of the following features: depth >2mm; Clark Level ≥IV; perineural invasion; poorly differentiated or undifferentiated; located on ear or hair-bearing lip.

Table 31: Comparison of AJCC 6th and 7th editions for SCC T-classification

AJCC sixth edition	
	Number (%) of excised SCCs (N=276)
T1 ≤2cm diameter	146 (52.9)
T2 2-5cm diameter	22 (8.0)
T3 >5cm diameter	7 (2.5)
Not classifiable from data available	101 (36.6)

AJCC seventh edition	
	Number (%) of excised SCCs (N=276)
T1 ≤2cm with fewer than 2 high-risk features*	34 (12.3)
T2 >2cm with fewer than 2 High-risk features OR tumour any size with ≥2 high-risk features	141 (51.9)
T3 Based on invasion of maxilla, mandible. Orbit, temporal bone rather than size	-
Not classifiable from data available	101 (36.6)
*>2cm; >2mm deep; PNI; Clark level ≥IV; poorly differentiated; ear or non-hair-bearing lip	

Of the SCCs with sufficient data to enable T classification, (n=175), 112 (64%) were less than 2cm in diameter and would only be classified as T2 when histopathology data was available based upon the presence of 2 or more additional high-risk features.

7.4.9. Tumour classification based on Brigham and Women's Hospital Criteria

Excised SCCs with sufficient data were classified according to the BWH staging, slightly modified according to how data was recorded in the 2006-7 dataset. As nerve calibre was not recorded in the dataset, all PNI was classed as a high-risk feature. Also, invasion recorded as subcutaneous was considered a high-risk feature.

The results are summarised in Table 32.

Table 32: Classification of excised SCC based on Brigham and Women's Hospital criteria

Brigham and Women's Hospital classification		
	Number (%) of excised SCCs (N=276)	**% of classifiable SCCs (N=137)**
T1 *No risk factors**	69 (25)	50.4
T2a *1 risk factor*	42 (15.2)	30.6
T2b *2-3 risk factors*	25 (9.0)	18.3
T3 *≥4 risk factors*	1 (0.4)	0.7
Not classifiable from data available	139 (50.4)	-
Total	276 (100)	100
*>2cm diameter; PNI; poorly differentiated; subcutaneous or beyond		

7.4.10. Outcome analysis

Outcome data was available for 351/375 (95.2%) of SCCs in total, and for 276/294 (93.8%) of excisions in 265 patients, the results for which are summarised in Table 33.

Table 33: Overall outcomes within 5 years of treatment for excised SCCs

Outcome	Number (%) with outcome
Local recurrence	17/276 (6.2)
Regional recurrence	9/276 (3.3)
Distant metastases	0/265 (0)
All-cause mortality	116/265 (43.8)
SCC-attributable death	4/265 (1.5)

Figure 49 is a flowchart in which the number and types of recurrences are broken down according to patients' mortality status at 5 years for both the entire SCC dataset (all specimen types) and for excision only. Overall mortality over the 5 years was high given the mean age of the study population, with 149 of the total 337 patients (44.2%) having died during the study period, with 138 (92.3%) of these dying from an unrelated or unknown cause.

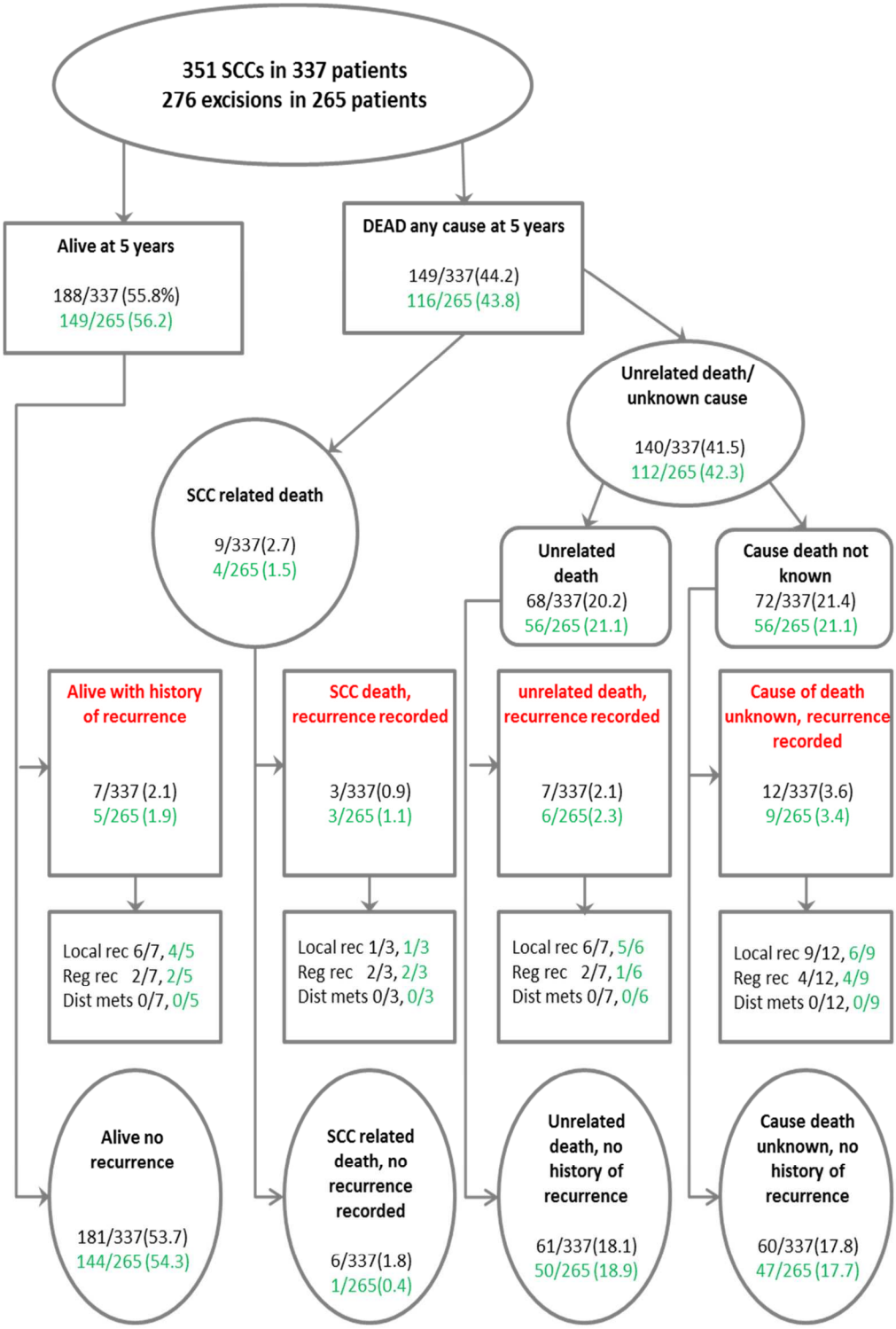


Figure 49: Flowchart of outcomes for SCCs (all specimen types in black, excisions only in green)

7.4.11. Outcomes according to AJCC7 and BWH T staging

Subgroup analyses were performed to compare outcomes between the AJCC classification and the BWH staging (Table 34).

Table 34: Comparison of outcomes based on AJCC (7) T2 staging and modified BWH staging

Number (%) with outcome								
Outcome	**AJCC7**			**Brigham and Women's Hospital T staging**				
	T1	**T2**	p-value (χ^2/ Fisher's test)	**T1**	**T2a**	**T2b**	**T3**	p-value (χ^2 for trend)
Local recurrence (SCC as unit of analysis)	1/34 (2.9)	13/141 (9.2)	0.31	4/69 (5.8)	4/42 (9.5)	5/25 (20)	0/1 (0)	**0.045**
Regional recurrence (SCC as unit of analysis)	0/34 (0.0)	7/141 (5.0)	0.34	0/69 (0)	3/42 (7.1)	3/25 (12)	0/1 (0)	**0.007**
Distant metastases (patient as unit of analysis)	0/33 (0.0)	0/135 (0.0)	-	0/65 (0)	0/41 (0)	0/24 (0)	0/1 (0)	-
All-cause death	12/33 (36.4)	67/135 (49.6)	0.18	25/65 (36.9)	24/41 (58.5)	16/24 (66.7)	0/1 (0)	**0.004**
Death attributable to SCC	1/33 (3.0)	2/135 (1.5)	0.48	0/65 (0)	2/41 (4.8)	0/24 (0)	0/1 (0)	0.548

For SCCs classifiable by AJCC7, there were no statistically significant differences in outcomes between T1 and T2 tumours (Fisher's test local recurrence p=0.31; regional recurrence p=0.34; SCC attributable deaths p=0.48; all cause deaths p =0.18).

When tumours were classified according to the BWH criteria, there was a statistically significant increased trend towards local recurrence (chi-squared test for trend, p=0.045), regional metastases (chi-squared test for trend, p=0.007), and death from any cause (chi-squared test for trend, p=0.004) with increasing substage from T1 to T2b. As only one SCC was classified as T3 it was not included in the analysis. There were only 2 deaths which were attributable to SCC in the group, both of which occurred in patients who had tumours classified as T2a according to BWH criteria.

7.4.12. Univariable and multivariable analyses

Local recurrence

Only perineural invasion and perivascular invasion appeared to have an association with local recurrence (Fisher's test p=0.05 and p=0.01 respectively); however, the variables were correlated (Fisher's test p<0.001), therefore they were assessed separately in the models. None of the additional variables were found to be significantly associated with local recurrence during the model fitting process. Therefore the only prognostic features that are independently associated with local recurrence are PNI and vascular invasion (Table 35).

Regional recurrence

Only diameter >2cm and vascular invasion appeared to have an association with regional recurrence (Fisher's test p=0.06 and p=0.085 respectively). There didn't appear to be a correlation between the two prognostic features (Fisher's test p=0.41), therefore the variables were included in the same multivariable model. None of the additional variables were found to be significantly associated with regional recurrence during the model fitting

process. However, when diameter and vascular invasion were included in the model together, the p-value for vascular invasion became non-significant (p=0.99). Therefore only a diameter >2cm was independently associated with regional recurrence (odds ratio 5.78, 95% confidence intervals 1.10 to 30.4) (Table 35).

SCC attributable death

Prognostic features that appeared to be associated with SCC attributable death were depth>2mm (Fisher's test, p=0.04), depth >4mm (p=0.06), PNI (p=0.01), vascular invasion (p=0.01), high-risk pathology type (p=0.05), peripheral histological margin ≤1mm (p=0.07), and deep histological margin ≤1mm (p=0.05). Due to the number of prognostic features identified from the univariable models, the variables were added in order of significance as identified in the univariable models. Depth >4mm had a marginally better fit in the univariable model than depth >2mm; however, only the comparison of 'missing' category versus 'no' was significantly associated with SCC attributable death for depth>2mm; and the same was seen for PNI, vascular invasion and high-risk pathology, therefore none of these features were included in subsequent models. Thus, the final model only included age, where increased age was significantly associated with increased odds of SCC attributable death (odds ratio 1.14, 95% confidence intervals 1.03 to 1.21) (Table 35).

All-cause mortality

Initially, the only prognostic feature that appeared to be associated with death from any cause was differentiation (Fisher's test p=0.01). However, during the model fitting process, age and gender were also found to be significantly related to all-cause mortality (Table 35). None of the additional variables were significantly associated with outcome, although vascular invasion had borderline significance in the multivariable model (p=0.062).

Table 35: Summary of prognostic features independently associated with outcome

	Odds ratio (95% CI)
Local recurrence:	
PNI (yes/no)	4.8 (1.2 to 19.3)
Vascular invasion (yes/no)	10.3 (1.6- 66.1)
Regional recurrence:	
Diameter (>2cm versus <2cm)	5.78 (1.10 to 30.4)
SCC attributable death:	
Age (in years)	1.14 (1.03 to 1.21)
All-cause death:	
Age (in years)	1.10 (1.07 to 1.13)
Gender (male versus female)	1.92 (1.15 to 3.2)
Poor differentiation	2.21 (1.23 to 3.98)

7.4.13. Summary of number of patients potentially eligible for the proposed trial

Patients will be eligible for recruitment into the proposed trial according to the T-classification of their SCC, which will be based upon a modification of the BWH staging criteria (see section 7.2.1 and section 7.4.9). Two scenarios are presented in Table 36:

(A) numbers are based on a modification of the basic BWH classification in which T2a tumours have one risk factor (diameter >2cm, level of invasion subcutaneous or more (although not including bony invasion), poorly differentiated; PNI), T2b have 2 to 3 of these risk factors, and T3 have 4 risk factors.

(B) In addition to the above risk factors, depth >4mm is included as one of the risk factors (section 7.2.1).

Table 36: Number of patients with excised SCCs potentially eligible for recruiting into trial (first randomisation)

Scenario for eligibility for entering first stage of trial	Number (%) of patients (N=131)
A) Brigham and Women's Hospital T2a/T2b/T3	66 (50.4)
B) Brigham and Women's Hospital T2a/T2b/T3 including >4mm depth as inclusion factor	82 (62.6)

In the second stage of the proposed trial eligible patients will be further randomised to receive either adjuvant radiotherapy or no adjuvant radiotherapy. Only SCCs that are classified as T2b and therefore have at least two potentially adverse prognostic features will be eligible for randomisation into the second stage of the proposed trial. Based on these criteria and from the total number of patients who have sufficient data with which to classify their SCC, the number of eligible patients who would potentially be eligible for the second stage of randomisation is summarised in Table 37.

Table 37: Number of patients with SCC potentially eligible for second-stage randomisation

Scenario for eligibility for entering second stage of trial	Number (%) of patients (N=131)
A) Brigham and Women's Hospital T2b/T3	25 (19.1)
B) Brigham and Women's Hospital T2b/T3 including >4mm depth as inclusion factor	40 (30.5)

Extrapolation of the above percentage to the total number of patients in the database gives an approximation of the number of patients that would potentially be eligible for randomisation into each stage of the proposed trial for each 12-month treatment period (Table 38).

Table 38: Approximate number of patients potentially eligible for randomisation into proposed trial based on SCC T-classification

	Approximate number of potential patients	
	2006-2010	**2010-20112**
A) Brigham and Women's Hospital T2a/T2b/T3:		
▪ First surgical randomisation	185	219
▪ Second ART randomisation	70	83
B) Brigham and Women's Hospital T2b/T3 including >4mm depth as inclusion factor		
▪ First surgical randomisation	223	264
▪ Second ART randomisation	109	128

7.5 Discussion

7.5.1. Numbers of SCC treated and demographics of patients

Cutaneous squamous cell carcinoma is a common nonmelanoma skin cancer. Over the two 12-month data collection periods 421 and 512 non-metastatic SCCs were submitted to the histopathology laboratory serving a population of approximately 1,070,000 people under the auspices of the Nottinghamshire Locality of the East Midlands Cancer Network. This represented an increase of 23% in the number of SCCs submitted and an 18.5% increase in the number of patients treated between 2006-7 and 2010-11, with an accompanying significant increase in the mean age of the patients treated from 76 years during 2006-7 to 78 years during 2010-11. There is likely to have been an increase in the size of the population at risk in Nottingham during the intervening years between the two datasets, but as this data was not examined it is not possible to say whether the incidence of SCC has also increased. However, the increase in the number of patients treated is an indication of an increased clinical workload with associated cost and health services planning implications.

There appeared to be more patients over 80 years of age in the most recent dataset, although overall there was no significant change between the two years in terms of age group distribution. Increasing incidence of SCC in older age groups has been noted in other studies around the world. In Ireland, the incidence of all NMSCs increased between 1994 and 2011, with significant increases in SCC annual percentage change for those aged 65 and above, in contrast to BCCs in which the most significant increases were in the younger age groups (Deady et al., 2014). A retrospective study of over 50000 NMSCs in New Zealand found that there had been a 1.1% increase in SCC incidence between 1999 and 2007, and that during that time it was men aged 80 and above who had the most significant increase in annual percentage change (APC) (3.65; $p<0.005$), contrasting with a concerning increase in APC for BCCs among younger people, particularly in females in the 40-49 year age group

(Brougham et al., 2011). The high-profile health awareness 'Sunsmart' campaign has been running in Australia since 1981 and it would appear that the benefits of this in relation to the falling incidence of SCC in younger people is now being realised, with reported stabilisation of SCC incidence rates in the under 50s (Staples et al., 2006), and a decrease in the number of SCCs treated in people aged under 45 years relative to the growth of the population (Fransen et al., 2012). In the UK, public health campaigns to promote sun awareness have lagged behind those in Australia; Cancer Research UK's 'SunSmart' skin cancer prevention campaign was instigated in 2003 (http://www.sunsmart.org.uk/about-sunsmart/). The slight increase in the number of over 80 year olds treated compared with other age groups in this study is interesting but needs to be confirmed with trends over a longer period of time. However, the findings may reflect greater sun awareness over recent decades, and the improved availability and use of sun-protection products among younger people. The regular application of sunscreen has been shown to have long term protective effects against developing SCC, although the evidence for a clear benefit against BCC and melanoma is less robust (Green et al., 1999, van der Pols et al., 2006, Green et al., 2010). It will therefore be interesting to see if UK trends over the next few years mirror those that are being seen elsewhere in the world.

In this analysis, there was a preponderance for the sun-exposed areas of the head and neck in both sexes, and an excess of tumours located on the legs in females and the ears in men, which is consistent with the findings from other studies (Buettner and Raasch, 1998) (Brewster et al., 2007b) and likely to be a reflection of the different clothing and hairstyles and exposure of skin from receding hair. Although men are more commonly affected by SCC than women, the results from this study have shown that more women than men are being treated by plastic surgeons, who are also significantly more likely to be treating larger tumours than their dermatology counterparts. It is recognised that plastic surgeons tend to be referred larger and more challenging lesions (Khan et al., 2013), and the reversal of the male to female

ratio in the patients treated by plastic surgeons may be a reflection of enhanced cosmetic concerns amongst women and their desire for minimal scarring on exposed areas such as the face. This would however, need to be confirmed with larger numbers of patients.

7.5.2. Adequacy of excision

Uncertainty about optimal clinical excision margins for SCCs that are surgically excised was one of the predominant issues that emerged from the clinician survey described in chapter 5. The adequacy of excision margins and their recording in the medical notes is one of the audit points specified in the 2009 updated UK BAD multiprofessional SCC management guidelines (Motley et al., 2002), and adequacy of resection is also identified as an area for research in the 2006 NICE guidance (National Institute for Health and Clinical Excellence, 2006). This may explain why the recording of clinical excision size on the pathology reports was so much more complete in the later dataset (2010-11) compared with the earlier one in which only 2.3% of excisions had this data recorded.

It would appear that generally the current margin recommendations are being adhered to, with a mean margin size of 4.5mm for smaller SCCs, and 7.8mm for larger ones (against recommendations of 4mm for small, well-defiend low-risk tumours and 6mm for larger and higher risk tumours). However, in this study the mean clinical margin for SCCs sited on the head or neck was smaller than that for SCCs located on the limbs or trunk, and suggests that in cosmetically sensitive areas there may be some compromise between tissue conservation and strict adherence to recommendations. This finding has also been noted in audits of plastic surgeons conducted after the introduction of the guidelines in 2002 (Staiano et al., 2004, Hemington-Gorse et al., 2006), and more recent audits have indicated that variation still exists among surgeons regarding adherence to guidelines in relation to the size of excision margins that are taken (Batchelor and Stables, 2006, Soueid et al., 2009).

Adequacy of primary excision is important, and perhaps especially so in areas where further intervention and reconstruction could compromise cosmesis and function further. Incomplete excision has been shown to be independently associated with regional metastasis in one study (odds ratio 2.0) (Mourouzis et al., 2009), and recurrence of 29% of re-excisions that contained residual tumour was noted in another study (Bovill and Banwell, 2012). Several studies have shown an association between incomplete excision and location in anatomically complex areas such as the ear, scalp, nose and cheek (Khan et al., 2013, Brantsch et al., 2008, Bogdanov-Berezovsky et al., 2005). The findings of this study concur with this. Seven of 213 (3.3%) of SCCs had histological involvement at either the peripheral or deep edge of the exxicsed specimen, of which three, located on the ear, cheek and neck, had involvement of both margins. Three of the SCCs that had involvement of one margin were located on the ear, and the other on the scalp.

The 3% of SCCs with margin involvement is is somewhat lower than the pooled incomplete excision rate of 8.8% (95% confidence intervals 5.3 to 13.0) in the 2343 excisions in 11 studies that was found in the systematic review of case series reported in chapter 4. However, there is lack of consistency in the literature about what is meant by completeness of exision; definitions, when provided, include the presence of tumours cells at the surgical edge, tumour cells at or within 1mm of the resected edge, tumour cells within one microscopic field (0.5mm), and others simply as ‘close to’ the margin. The adequacy of excision of SCCs that do not transect the surgical edge but which are within 1mm is a grey area, and their management is a cause for debate among clinicians. In this study, 27 (13.6%) of excised SCCs were either at or within 1mm of the peripheral or deep edge and would therefore not be eligible to be randomised into the second adjuvant radiotherapy stage of the proposed trial, which will be discussed in greater depth in chapter 8. This study indicates that the deep margin is significantly more likely to be involved than the peripheral margin. Six of the seven

transecting SCCs (86%) involved the deep margin which is in accordance with a recent study in which 92% of incomplete SCC excisions by plastic surgeons were incomplete at the deep margin, even though only 32% had involvement of the peripheral margin (Khan et al., 2013). There is currently no guidance in the UK management guidelines (Motley et al., 2002) regarding deep clinical margins , but as these margins are more frequently implicated than peripheral margins it is perhaps prudent to have a high suspicion of residual microscopic disease at the deep margin and excise down to the next fascial plane beyond apparent macroscopic appeararance (Khan et al., 2013). On the basis of these findings and for the purposes of the proposed trial (chapter 8), it will be important not to focus solely on the definition of the peripehral clinical margin at the the expense of the deep margin; this too will need to be clearly defined and adhered to in order to minimise the number of potentially eligible SCCs that are excluded from the second ART randomisation stage of the trial because the deep histological margin is less than 1mm.

7.5.3. Classification of SCCs

Although only a small percentage of SCCs recur, it is important to identify those that are at greatest risk of recurring at an early stage. Currently the definition of 'high-risk SCC' is very variable but the development of a prognostic model is an important step toward targetting the most appropriate treatments to those who are most likely to benefit from them, for example adjuvant radiotherapy and nodal staging. In the most recent American Joint Committee on Cancer (AJCC7) classification, primary SCCs are classified as being T1 or T2, with higher risk T2 tumours being those greater than 2cm in horizontal diameter, or smaller than 2cm but with 2 or more additional characteristics associated with poor prognosis, features which were not incorporated into previous editions: depth >2mm; Clark level ≥IV;perineural invasion; poorly differentiated or undifferentiated; primary site on ear or hair-bearing lip (Edge and Compton, 2010). This has resulted in a

significant increase in the number of SCCs that have been upgraded to T2 tumours from 8% to more than 50%. Although an improvement on previous classifications in an attempt to stratify patients more accurately, the new classification is not without criticism, omitting several variables associated with high-risk disease, such as host immunosuppresion, previously treated tumours, and the presence of chronic inflammation or location in burns and scars, and there is also some confusion regarding the precise lip location (hair-bearing or non-hair bearing) as defined in the AJCC manual (Buethe et al., 2011a, Edge and Compton, 2010). An alternative tumour staging system (BWH) has been proposed in an attempt to offer better prognostic stratification of AJCC7 T2 tumours, in which T1 tumours have no risk factors but are upstaged to T2a in the presence of either perineural invasion or poor/undifferentiated or invasion beyond subcutaneous fat, T2b tumours have 2-3 risk factors, and T3 tumours have bone invasion or have all 4 risk factors (>2cm diameter, PNI, poorly differentiated and invasion beyond subcutaneous fat) (Jambusaria-Pahlajani et al., 2013, Karia et al., 2013).

Using the modified BWH classification, the majority (81%) of the 137 SCCs that had sufficient data to classify fell into the T1 and T2a categories, with the remaining 19% being T2b or T3. This corresponds with the breakdown of SCC according to the original paper in which the BWH scheme was proposed (Jambusaria-Pahlajani et al., 2013), in which 52% of SCCs were T1, 26% were T2a, 19% were T2b and 2% were T3, although higher than the proportion of T2b and T3 SCCs in their subsequent paper, in which only 5% of SCC were classified as T2b or T3 (Karia et al., 2013). This may be because the definition of PNI in the second paper was more stringent, and only PNI was only considered a risk factor if the calibre of the involved nerve was greater than 0.1mm (Karia et al., 2013).

7.5.4. Tumour features associated with prognosis

SCCs spread laterally and vertically and growth may become discontinuous once deep extension has occurred, which can result in even deeper local

extension, in-transit metastases, and nodal metastases. The following factors have been correlated with poor prognosis for recurrence and metastases:

Tumour diameter

Rowe et al (1992) in an analysis of case series found that the local recurrence rate for tumours >2cm was 15.2% compared to 7.4% for those less than 2cm, and that metastatic rates were tripled (30.3% vs 9.1%). Other studies have corroborated these findings. Kraus et al (1998) found that of 16 patients with regional lymph node metastasis, 13 (81%) had primary tumours larger than 2cm compared to 24% in historical controls, although of the total number of metastatic tumours they examined in their population, tumour size data was only available for a limited number as most had been initially treated at other centres. A threshold size of 2cm for increased propensity to recur and metastasise has been suggested by several studies (Cherpelis et al 2002; Griffiths et al 2002; Dinehart et al 1989; Breuninger et al 1990). In a prospective study by Clayman et al (2005), lesion size greater or equal to 4cm, along with evidence of perineural invasion and invasion into deep tissues were the factors most strongly associated with diminished 3-year disease-specific survival. However, one study of 266 patients with SCC metastatic to the regional lymph nodes found that most of the primary tumours in the study population were less than 2cm in diameter (Veness 2006) and concluded that size alone is probably not an independent predictor of outcome and other prognostic features also need to be taken into consideration (Veness 2006).

Tumour depth

Some experts believe that the Breslow tumour thickness of 4-5mm (measured from the top of the granular layer to the deepest point of invasion) and a Clark level of IV or V (invasion of reticular dermis and subcutaneous fat) are the most important prognostic factors for SCC beyond which the rate of

metastasis increases significantly (Kraus et al 1998; Dinehart et al 1989; Breuninger et al 1990). However, the reporting of these measurements has often been overlooked by pathologists (Khanna 2002). Breuninger et al (1990) found that in their series of 673 tumours with a median follow-up period of 5.3 years there were no metastases at all in the 325 tumours which were less than 2mm thick, compared to 13 in the 288 (4.5%) tumours between 2 and 6 mm thick, and 9 of the 60 (15%) of tumours greater than 6mm in depth, and on the basis of these findings they designated 3 risk groups : 1. 'No risk' (less than 2mm); 2. 'Low-risk' (2-6mm deep); and 3. 'High-risk' (>6mm deep).

A similar correlation between tumour thickness and metastatic risk has also been seen in other prospective studies (Breuninger et al 1997; Brantsch et al 2008). For tumours less than 4mm deep or Clark level I-III a metastatic rate of 6.7% was found compared to 45.7% in those tumours greater than 4mm or Clark level IV or V in the analysis of series by Rowe (1992). The accumulation of evidence in support of the importance of tumour depth as a prognostic factor has now been incorporated into the revised American Joint Committee on Cancer (AJCC) Tumour, Node and Metastasis (TNM) staging system (AJCC 2010), as the previous AJCC staging system assigned horizontal diameter as being the only important variable in the T stage, a staging system which was much criticised (Veness 2008).

Histologic differentiation

Several studies have indicated that poorly-differentiated SCCs have a worse prognosis than those which are well-differentiated on histology (Johnson et al 1992; Mohs 1978; Eroglu 1996). In one series of patients with metastatic SCC, significantly more patients had poorly-differentiated lesions (44%) compared to those with well-differentiated SCCs (5%)(Cherpelis et al 2002), which compares with the 33% metastatic rate for poorly differentiated lesions compared to 9% for well-differentiated SCCs shown by Rowe et al (1992). Breuninger et al (1990) found that there was a rapid increase in metastatic

rate from 4% to 17% between SCCs classed as G3 (poorly differentiated) and G4 (undifferentiated). However, Rowe et al (1992) suggested that as 64% of metastatic lesions in their analysis were well-differentiated, the histologic differentiation may be of limited importance as a prognostic factor on its own. More recently however, it has been indicated that the presence of desmoplasia (fine branches of tumour cells at the periphery with surrounding dermal stromal reaction) may be a particularly strong prognostic feature with high risk of recurrence and metastasis (Breuninger et al 1997). The authors found that desmoplastic SCCs were often more advanced at diagnosis and thicker than 'common' SCCs, and that those tumours in their 2-5mm thick 'low-risk group' which did metastasise had desmoplastic features.

Anatomic site

SCCs in the region around the ear and lower lip have particularly high local recurrence rates and metastatic rates compared to those elsewhere (Afzelius et al 1980; Lee 1996). A local recurrence rate of 18.7% and metastatic rate of 11% were shown by Rowe et al (1992) for SCCs located in the peri-auricular region, rates which were more than double those seen elsewhere. Tumours in the region of the lip also had a higher local recurrence rates (11%) and a markedly higher metastatic rate (14%) than tumours located at other sites. Even higher rates are seen for SCCs located in non-sun-exposed areas of the body and those arising in chronic ulcers, sinuses and chronic inflammation, and in areas of radiation or thermal injury (Rowe et al 1992). Two studies with 5 year follow-up had an overall metastatic rate of 38% for SCCs arising in such high-risk sites (Novick et al 1977; Ames et al 1980).

Perineural Invasion

Perineural involvement (PNI) is not a common feature of SCC of the skin, occurring in approximately 5% of patients with the tumour, and is frequently an incidental finding on post-operative histology examination (Veness 2006).

However it is a feature which has been associated with significantly higher metastatic rates and poor prognosis (Cherpelis et al 2002; Frierson and Cooper1986). Ballantyne et al (1963) reported that of their 34 cases with PNI, only 10 were alive and disease free 2 to 5 years later. A 47% local recurrence rate and 35% metastatic rate with significantly reduced survival after treatment by surgical excision were reported by Goepfert et al (1984). Improved prognosis after treatment of PNI by Mohs micrographic surgery has however been found by Cottel (1982), who reported no local recurrences and a 6% metastatic rate when the same types of lesions were treated by this modality, although only seventeen cases were reported.

Variables associated with outcomes in this study

In the univariate analysis in this study, an increase in odds of local recurrence was seen in patients perineural invasion, which is consistent with other studies (Jambusaria-Pahlajani et al., 2013, Veness et al., 2006). Vascular invasion was associated with PNI, but also was independently associated with an increase in odds of local recurrence. The only variable that was independently associated with regional metastasis in this study was diameter greater than 2cm. As discussed above, diameter as an independent factor associated with the risk of metastasis has also been described in several other studies (Cherpelis et al 2002; Griffiths et al 2002; Dinehart et al 1989; Breuninger et al 1990).

Although there were several variables on univariate analysis that appeared to be associated with SCC related death, on multivariable analysis only age was found to be significantly related. However, death from any cause appeared to be significantly associated with age, male gender and a poorly differentiated tumour.

Unlike some of the studies mentioned above, an association between tumour depth and outcome was not found in this study. Similarly, location on the lip

or ear was not found to be significantly associated with outcomes in this study, in contrast to the studies mentioned above, and the results of the systematic review and pooled analysis described in chapter 4, in which a significant association was found between location at the ear and both local and regional recurrence. It should, however, be noted that the odds ratios for some of these variables were large, with very wide confidence intervals, and therefore likely to be a reflection of the small numbers of patients experiencing outcomes. These results therefore need to be interpreted with caution.

The high-risk features used in the AJCC7 and BWH classification schemes are not completely identical to those defined by NICE guidelines as being high-risk for the purposes of MDT referral and patient management and treatment, in which tumours greater than 4mm in depth and those extending into subcutaneous tissue (Clark level V) are considered to be high-risk (Brewster et al., 2007b).The British Association of Dermatologists (BAD) multiprofessional guidelines also adopt these criteria in their stratification of low and high risk SCCs (Motley et al., 2002) and they are adopted as high-risk features in the Royal College of Pathologists (RCPath) minimum dataset (Chaudhuri et al., 2006) . Currently the evidence that the presence of lymphovascular invasion as an independent risk-factor for metastasis and death is limited (Moore et al., 2005, Mourouzis et al., 2009), but its presence is listed as a high-risk pathological feature in the RCPath minimum dataset. Similarly, desmoplastic, acantholytic, spindle, metaplastic, sarcomatoid, adenosquamous growth patterns and SCCs with an adjacent area of Bowens disease are considered to be high-risk features by the RCPath and National Clinical Guidelines (Chaudhuri et al., 2006, Motley et al., 2002)

7.5.5. Outcomes after treatment

Although a common tumour, recurrences from SCC are fortunately rare although a small subset do go on to have local recurrence after treatment, or experience spread to the regional lymph nodes or distant organs, and some

may die as a direct result of their disease. In the present study, 6% of SCCs recurred locally during the 5-years after treatment, a figure similar to the 5% local recurrence seen after conventional excision reported in the systematic review and pooled analysis of case series of treatments for SCC earlier in this thesis (chapter 4), and the 5% local recurrence reported in a large 10 year prospective cohort study of 985 patients (Weinstock et al., 1992).

Metastasis to regional lymph nodes occurred in 3% of excised SCCs, comparable with the 2-3% figure for nodal metastasis recently reported over a 10 year study period in a retrospective study of 6164 patients (Brougham et al., 2012), and the 4% after surgical excision in the pooled analysis of case series reported in chapter 4 of this thesis.

Overall mortality from any cause was high with nearly half of the study population having died over the 5 years, although this is not entirely surprising given the advanced age of the group. However, deaths that were attributable to SCC were rare with less than 2% of the study population dying as a result of their disease, which is similar to the figures reported in other studies (Brantsch et al., 2008, Weinstock et al., 1992), and slightly less than the 4% figure found from the pooled analysis of case series of surgical excision, which may be partly explained by possible misrecording of deaths as being due to SCC in what were mostly restrospective studies (chapter 4). Inaccurate death certification has been recognised as a particular problem for nonmelanoma skin cancer so this data should be interpreted cautiously (Weinstock et al., 1992). In the 6 patients with excision in whom death was attributed to SCC, two had involvement of regional lymph nodes and one had local recurrence. In this study, no distant metastases were reported within 5 years of treatment. This is not entirely unexpected as distant metastases are rare in cutaneous SCC; only two studies that were included in the systematic review of observational studies specifically reported distant metastases after surgical excision, with one of 211 patients experiencing a distant metastasis in

one study (Knox et al., 1967) and no distant metastasis in the other (Donaldson, 2002).

Outcomes after different treatment modalities were not assessed in this study as most were treated by surgical excision and there were inadequate numbers which were known to have been treated by other modalities. It is also possible that SCCs that were treated by destructive modalities such as cryotherapy or cauterisation and electrodesiccation did not have any pathology recorded on the database. A recent prospective study of consecutive nonmelanoma cancers found that recurrence rates were similar after excision and Mohs surgery, even when the conventional risk factors for recurrence were adjusted for (Chren et al., 2013), which is supported by the systematic review and pooled analysis of treatments for SCC in which there was significant overlap of confidence intervals between different treatment modalities (chapter 4).

The main reason that a modified BWH classification will be used in the proposed trial is to help define the highest risk SCCs which will be eligible for randomisation to receive ART or not. The original papers describing this alternative scheme found that although the highest T2b and T3 stages made up only a small percentage of the overall cohort, they accounted for 60% of the poor outcomes, including 70% of nodal metastases (Karia et al., 2013). The results from this research found that the proportion of patients who had local recurrence, regional recurrence or who died from any cause rose with increasing BWH stage from T1 to T2b. Both SCC-attribuatble deaths occurred in stage T2a patients, and only one patient had an SCC classifiable as T3 in this study. As the number of SCCs that had adequate data to be able to classify them was small compared with the original paper (Karia et al., 2013), the results of this study need to be be interpreted cautiously. Nevertheless, given this trend and the data available from the other studies (Jambusaria-Pahlajani et al., 2013, Karia et al., 2013, Schmitt et al., 2014), using a modification of the BWH classification would seem a reasonable approach to identifiying those

SCCs that are at greatest risk of having a poor outcome and therefore being eligible for the second randomisation stage of the proposed trial.

7.5.6. Implications for future research

The current study forms part of the feasibility work for a future RCT into management of high-risk SCCs. By comparison of the AJCC7 and modified BWH staging systems, the results indicate that on the basis of the T classification, approximately 50% of patients would be eligible to be randomised into the first surgical stage of the trial (51.9% of classifiable SCCs were AJCC7 T2 and 50.4% were BWH T2a, T2b or T3). By including depth greater than 4mm as one of the BWH staging high-risk factors, the percentage of eligible SCCs would increase to 62.6%.

For the second ART randomisation, use of the modified BWH classification would allow identification of the highest-risk SCCs with at least two poor prognostic features and is therefore more useful than AJCC7 staging in the proposed trial. Based upon modified BWH staging, 37.9% of T2a, T2b or T3 identified for the first randomisation stage would then be eligible to be randomised into the second stage (19% of the original total); increasing to 48.8% if depth >4mm is included (30.5% of original total). Because information about several variables is required to be able to completely classify excised SCCs, incomplete data recording on the pathology database meant that only 50% of all excised SCCs could be completely classified. In order to identify eligible SCCs for the proposed trial it will therefore be necessary to undertake an initial punch biopsy with complete recording of variable data so that SCCs can then be classified. Extrapolating the results of the T-classification to the entire population of SCC patients treated during the 12-month period in Nottingham would mean that during 2006-7 approximately 185 of 357 patients would have been potentially eligible to be randomised into the first stage of the trial, and 70 into the second stage, and that during 2010-11 there would have been approximately 219 patients of 423, and 83 patients eligible for each stage respectively. By including depth as

a risk factor, approximate numbers eligible would have increased during 2006-7 to approximately 223 and 109 for first and second randomisation stages respectively, and during 2010-11 to 264 and 128 respectively. These figures are based on the assumption that in the proposed trial all tumours would be classifiable, and that the percentage for each T classification would be similar to that found in this study.

It is envisaged that these results may be extrapolated to other centres in the UK based on the size of the population served, in order to calculate the number of centres that would be required to participate in the trial. The number of participants needed to be recruited will in turn be based on powering calculations, which will be informed by the number of those who experienced adverse outcomes over the course of the five years after treatment.

A limitation of this study is that the impact of the patients' immune status on outcomes was not assessed as this data was generally not recorded on the pathology database. Nevertheless, this would not affect the assessment of the number of potentially eligible SCCs for entry into the trial as immunosuppressed patients would not be excluded from the trial.

7.5.7. Conclusion

Further elucidation of the inter-relationship between the various prognostic features and outcomes will require large prospective studies to be conducted and the main objective of this part of the research was to determine the types and numbers of SCC that are treated in order to guide the design of such a study. This work has given insight into the demographics of the treated population in Nottingham, and an overview of the approximate number of patients from this large regional centre that would potentailly be eligible for entry into the proposed randomised trial, based on the classification of their SCCs according to the presence of various prognostic features.

However, the number of potentially eligible patients does not simply equate to the number who will ultimately be randomised in the definitive trial. Potential participants may for various reasons be reluctant to take part in the proposed trial. In the next chapter, drivers and barriers to recruitment will be explored in order to assess what factors are likely to affect hypothetical willingness to take part, and what lessons can be taken forward when designing the trial in order to optimise recruitment among potential participants.

CHAPTER 8:

FEASIBILITY STUDY

WITH PATIENTS

8 FEASIBILITY STUDY WITH PATIENTS

8.1 Abstract

Introduction:

Recruitment into RCTs can be challenging, particularly in cancer studies and in those in which the target population is predominantly elderly. With the aim of identifying potential drivers and barriers to recruitment to a proposed two-stage trial of SCC treatment, a feasibility study comprising a questionnaire and focus group was conducted with patients who had been treated for SCC within the previous 12 months, in order to learn lessons from their experiences and pre-existing knowledge and to inform the design of the proposed trial by incorporating issues that are important from the patients' perspective.

Methods:

In the first instance, SCC patients were sent a questionnaire assessing hypothetical willingness to take part in each stage of the proposed RCT. Patients' experiences of treatment and attitudes to research were explored in depth in a focus group. Thematic framework-analysis of data focussed on four overarching themes: knowledge of SCC; experiences of treatment; attitudes towards research; attitudes towards randomisation.

Results:

Generally, patients had poor understanding of SCC but would like to be better informed. Patients were not overly concerned about randomisation into the surgical arms of the first stage of the trial, although this would depend on the location of the tumour, but they expressed more concerns about the second-stage involving adjuvant radiotherapy. 71% of participants were hypothetically definitely or probably willing to be randomised into the first surgical stage, and 58% into the second ART stage. However, there was confusion about the concept of randomisation and clinical equipoise.

Conclusions:

The study has given insight into the proposed RCT from patients' perspective, and identified issues which will need to be taken into consideration when presenting the definitive trial if recruitment in a predominantly elderly population is to be optimised. In particular, the concept of randomisation will need thorough explanation and careful presentation of the treatment options in order to establish patient equipoise, especially for the ART stage of the proposed trial.

8.2 Introduction

This chapter describes feasibility work which was conducted with patients representative of potential participants in a future RCT of SCC treatments. The scenarios provided to patients in the questionnaire were based on the results of the survey work described in chapter 5, in which areas of treatment uncertainty of clinical importance were delineated by clinicians and from which possible trial scenarios were identified for further discussion and development with multidisciplinary collaboration. In this study, the acceptability of excision of SCC with different sized excision margins followed by adjuvant radiotherapy or no adjuvant radiotherapy has been explored as these were among the questions that were considered to be important by clinicians and which formed the basis of a trial proposal (Chapter 6). However, the willingness of patients to participate in such a study is unknown. This study has provided the opportunity to explore issues that are important to patients with regard to their diagnosis, treatment, and the information they would like to receive, and to gain insight into their understanding of the clinical research process and barriers and facilitators to their potential participation in a RCT in the future which would need to be taken into account when designing such trials.

8.2.1. Why it was important to conduct this study

It is recognised that recruitment into multi-centre RCTs can be difficult, with fewer than a third reaching their recruitment target and more than half requiring extension (Watson and Torgerson, 2006). Recruitment has been shown to be particularly problematic in cancer trials; only 24.9% of eligible patients with lung cancer were recruited into a trial involving adjuvant chemotherapy (Spiro et al., 2000), and only 43% of eligible patients with metastatic breast cancer in a trial of psychosocial support (Goodwin et al., 2000). Apart from the funding and ethical implications, this may lead to type II

error, in which it is concluded incorrectly that there is no significant difference between the treatment arms due to a lack of power from an inadequate sample size (Freiman et al., 1978).

The incidence of non-melanoma skin cancers increases with age, with approximately 80% occurring in people over 60 years, (Diffey and Langtry, 2005) but the recruitment of older patients into clinical trials can be particularly challenging. It is reported that only a quarter to a third of potentially eligible older people are enrolled into trials (Townsley et al., 2005); this may significantly impact upon external validity. From the retrospective case series of SCCs treated in Nottingham which was described in chapter 7, the average age at presentation was found to be 75 years. The RCT proposed and which will be discussed in greater detail in chapter 9 is therefore going to require successful recruitment from a largely elderly population.

As there have been no previous RCTs specifically addressing this type of skin cancer, it is therefore important to examine the beliefs and experiences of a population representative of potential RCT participants. This will help to identify possible barriers and drivers to recruitment, thus facilitating the design of the trial and assessment of the resources required.

8.2.2. Overview of the study design

The importance of participant involvement in the design and conduct of trials has been increasingly recognised over the last two decades and is now actively encouraged (Donovan et al., 2002b). For example, participants were involved in the design and conduct of the prostate testing for cancer and treatment (ProtecT) feasibility trial, and results from the qualitative work that were embedded within the study were incorporated into the design of the main trial and significantly improved recruitment rates (Donovan et al., 2002a).

Information relating to participants' attitudes to particular aspects of the trial and their potential willingness to take part may be gathered in several ways.

Structured questionnaires, in-depth interviews and focus groups are frequently used for this purpose (Mao et al., 2014, Kim et al., 2014, Wisinski et al., 2013, Judge et al., 2013, Leighton et al., 2012, Linden et al., 2007).

Prospective Preference Assessment

In this study, a combination of a mailed questionnaire with open and closed questions and a focus group was used to collect data from the study population. The design of the questionnaire was based upon the prospective preference method (PPA) described by Halpern which was developed as method by which the motivations and concerns about enrolling into a planned trial could be evaluated prior to actual recruitment and thus assess whether there is enthusiasm among potential participants (or clinicians) to take part (Halpern, 2002). Prospective preference assessment has been used to forecast recruitment rates in other studies (Halpern et al., 2003, Shah et al., 2012, Creel et al., 2005).There are several stages involved in PPA: description of the hypothetical trial; testing participants' understanding of the vignette; open-ended questioning to evaluate motivators and barriers to taking part in the trial; using ordinal response scales to evaluate potential willingness to participate in the trial if it were to commence in the near future. Eliciting whether participants have a strong preference for the treatment options or not is an important element of the assessment and has been shown to correlate with willingness to participate in RCTs (Mills et al., 2003, Wragg et al., 2000). This study is a modification of this method in that it the vignette was not administered by telephone or in a face-to-face interview, but was sent by mail prior to completion of the questionnaire. Participants' understanding of the proposed trial was therefore not assessed before the survey was completed.

Focus Groups

A focus group may be defined as "a group of individuals selected and assembled by researchers to discuss and comment on, from personal experience, the topic that is the subject of the research" (Powell and Single, 1996). Originally used in media research to examine the effects of films and

television programmes in the 1950s, they have become popular in health research over the past three decades as a tool to investigate the public's understanding of illness, health-related behaviours and health education messages (Kitzinger, 1995). They may be useful at various time points throughout the life of research programme; in the preliminary stages, during the main study, or after completion to assess impact and generate ideas for further research (Woolfall et al., 2014, Kreuger, 1988, Ersser et al., 2013).

Unlike group interviews, focus groups promote self-disclosure among participants that may not otherwise be revealed from individual interviews or surveys, and this is particularly the case when the participants perceive themselves to have similarities with others in the group and in a non-judgemental environment. By sharing experiences and through discourse with others who may have a different perspective, participants may start to think about an issue slightly differently than they would have done prior to discussion with others, thereby offering the potential for richer data to be gathered and greater exploration of the research question.

In this study a focus group is used in combination with the questionnaire, a form of methodological triangulation in which more than one method is used to collect data. Although the data collected is different, the methods complement each other thereby increasing the validity of the data and the utility of the findings (Denzin, 1978).

8.2.3. Thematic Framework Analysis

Thematic framework analysis is a relatively recent approach towards the analysis of qualitative data that was developed in the 1980s by social policy researchers at the National Centre for Social Research, but is becoming increasingly popular in health-related research (Ritchie and Spencer, 1993). It is a highly-structured matrix-based method that is particularly suited to research that is time-limited and that has clearly defined goals from the outset.

There are five stages to thematic framework analysis, with involvement of at least two people:

- Familiarisation with the data by reading and re-reading the content
- Construction of thematic framework reflecting the objectives of the research and based upon *a priori* issues but developed and refined as necessary as the process continues
- Indexing the data using codes to identify pieces of data belonging to the themes
- Charting the coded data into the thematic chart
- Mapping and interpretation of the data by looking for patterns, associations and explanations in the data.

Critical reflection is a key component throughout this process with researchers making reflexive notes, impressions of the data and recording thoughts about the analysis, thus allowing for the development and refinement of the analytical framework to be made in an iterative manner until the final framework is agreed and no additional codes emerge.

An advantage of this method is its flexibility as it is not aligned to any one particular epistemological, philosophical or theoretical approach and can be adapted for use with many different qualitative approaches in which the generation of themes is an important component (Gale et al., 2013). It is particularly useful for analysis of textual data, for example from interviews and transcriptions of focus groups, allowing comparison and contrasting of data by theme across multiple cases. Not all research questions are necessarily best answered through thematic framework analysis; for example, some research may call for the generation of grounded theory (a generalizable concept gained inductively rather than deductively from the data to help understand the social world) which 'emerges' from the data through rigorous and structured analysis and constant comparison between cases without an *a priori* framework (Glaser and Strauss, 1967).

As a method of analysis, a thematic framework approach is therefore ideally suited to this study in which the goals of the research are defined at the outset, in this case to support the development of a future trial, allowing the research objectives to be directly addressed whist also being strongly rooted in the responses of the study participants.

8.2.4. Objectives of this study

The objectives of this study were:

- To evaluate potential barriers to successful recruitment into a proposed future two-stage RCT of SCC surgery and adjuvant radiotherapy.
- To assess likely willingness of patients to be randomised into the proposed RCT.
- To explore current understanding of their condition, and clinical research generally in people previously treated for SCC, with a view to developing appropriate participant information resources for the proposed RCT.

8.3 Methods

8.3.1. Participant sample

A purposive sample of patients with cutaneous SCC who had been treated by one of the consultant dermatologists at Nottingham University Hospitals NHS Trust between 1 January 2012 and 31 December 2012 were sent a letter from the clinical care team inviting them to take part in the study, along with a participant information sheet (Appendix 5) explaining the purpose of the study. Private patients were excluded as Research and Innovation approvals were for the Nottingham University Hospitals to act as a Participant Identification Centre for NHS patients only. Consent to take part was implied by return of a reply slip allowing the research team to contact them. A minimum sample size of 20 questionnaire respondents was set as this was felt to be feasible number and would allow for a broad range of opinions to be canvassed.

8.3.2. Ethical approval

Ethical approval for the study was granted by the Proportionate Review Sub-Committee of the NRES Committee West Midlands –Coventry and Warwickshire (REC reference 13/WM/0051) (Appendix 4). Research and Innovation approval was given by the Nottingham University Hospitals NHS Trust in its capacity as a Participant Identification Centre, and the study was included on the NIHR Clinical Research Network Portfolio.

8.3.3. Questionnaire and focus group

A postal questionnaire with open and closed questions relating to the design of the proposed RCT and hypothetical willingness to be randomised to each stage was designed. Members of the UK Dermatology Clinical Trials Network (UKDCTN) Patient Panel piloted the questionnaire and provided feedback during a workshop session at their annual training day.

The questionnaire was sent to potential participants identified by the dermatologist from their patient list and who had been treated for SCC during 2012. Participants were asked to return their completed questionnaire within 14 days of receipt (Appendix 6). Prior to filling in the questionnaire, participants were first asked to read the accompanying trial scenario which explained the current uncertainties about what size of excision margin is optimal and about which patients may or may not benefit from having additional radiotherapy. This information also explained the process of randomisation, describing randomisation as being 'the best method of producing the fairest results' in RCTs.

In the questionnaire, participants were asked to rate their willingness to participate in the proposed trial on a five-point scale (definitely yes, probably yes, unsure, probably no, definitely no) and asked to explain their reason in an open-ended format. They were then asked to indicate if they had a strong preference for one of the treatment arms described over the other, again with the opportunity for further elaboration.

Demographic data was collected on the participants' age, employment status and the highest educational level attained.

At the end of the questionnaire, participants were asked about their willingness to take part in a focus group, designed to explore patients' attitudes to research and their condition generally, and to discuss issues around the trial itself in greater depth. Respondents who expressed an interest in participating in the focus group were telephoned by the research team and invited to take part.

Seven participants consented to take part, so one focus group was held, facilitated by two researchers. Those who took part were asked to respect the confidentiality of the other participants outside the setting of the focus group, and were assured that the transcribed recording would be anonymised and that participants would not be identifiable from any quotes subsequently

used. All participants signed a consent form before the discussion commenced (Appendix 7).

Discussion was based around a broad topic guide (Appendix 8), which included willingness to take part in clinical research generally, willingness to participate in each stage of the two-stage trial being proposed and possible barriers to taking part in research. Participants' use of information resources and knowledge of their condition was probed to ascertain the needs of participants in the proposed RCT in terms of information provision. The focus group lasted approximately 90 minutes and was recorded using digital recording equipment and transcribed in full by the principle researcher, with consultation with a second researcher where necessary.

8.3.4. Qualitative data analysis

Qualitative data from the questionnaires and focus group were analysed using a Thematic Framework Analysis approach (Pope et al., 2000, Ritchie and Spencer, 1993). An initial *a priori* thematic framework was constructed from the literature on clinical treatment and clinical trial recruitment, containing themes on knowledge of SCC, treatment experiences, attitudes towards research and understanding of randomisation. The framework was a simple model constructed selectively to address the research question, and reflecting the straightforward purpose of this research. Subtopics were amended if there was an excess of data or if no data were captured for a particular theme. A thematic map was generated to reflect the content of the focus group discussion and questionnaire responses and to generate insight into recruitment to the proposed trial (See Figure 50). Data from the questionnaires and focus groups were coded, indexed and charted onto the thematic framework for interpretation according to the research objectives (as per example in Table 39). This was done by the principle researcher and checked by a second researcher. Coding was 'broad-brush' and largely descriptive to reflect the straightforward research aims.

Table 39: An example of the indexing matrix

THEME 1 – TREATMENT					
	1.1 – Diagnosis	1.2 – Initial treatment	1.3 – Problems	1.4 – Concerns	1.5 - Support
Q'airre participant 1	Data reported/ summarised…… [lines x-y]	Data reported/ summarised…… [lines x-y]			
Q'airre participant 2	Data reported/ summarised…… [lines x-y]	Data reported/ summarised…… [lines x-y]			
…					
Focus Group 1	Data reported/ summarised…… [transcript lines x-y]	Data reported/ summarised…… [transcript lines x-y]			

8.3.5. Quantitative data analysis

Demographic data were analysed using SPSS 21 statistical software. Willingness to participate in both or one of the stages of the proposed trial was evaluated as a three-category variable: 1) Definitely willing to participate 2) probably willing or unsure 3) Probably or definitely unwilling to participate (not willing). The treatment preference variables were dichotomised into the categories 'strong preference' and 'no strong preference'.

The association of age, gender, employment status and educational level with willingness to be randomised into the stages of the proposed trial and strength of treatment preference was examined. Age was analysed as a continuous variable. Employment status was categorised as 'employed', 'not working due to ill-health', 'retired' or 'otherwise not working'. Education was categorised according to the highest educational level attained as either school (no formal qualifications, school certificate, 'O' or 'A' levels) or higher education (university degree or professional).

Statistical significance of variables was assessed by Chi-square probability or Fisher's test with 2-tailed p-values. Differences between means were

assessed with independent samples T-test. P values of ≤0.05 were considered statistically significant.

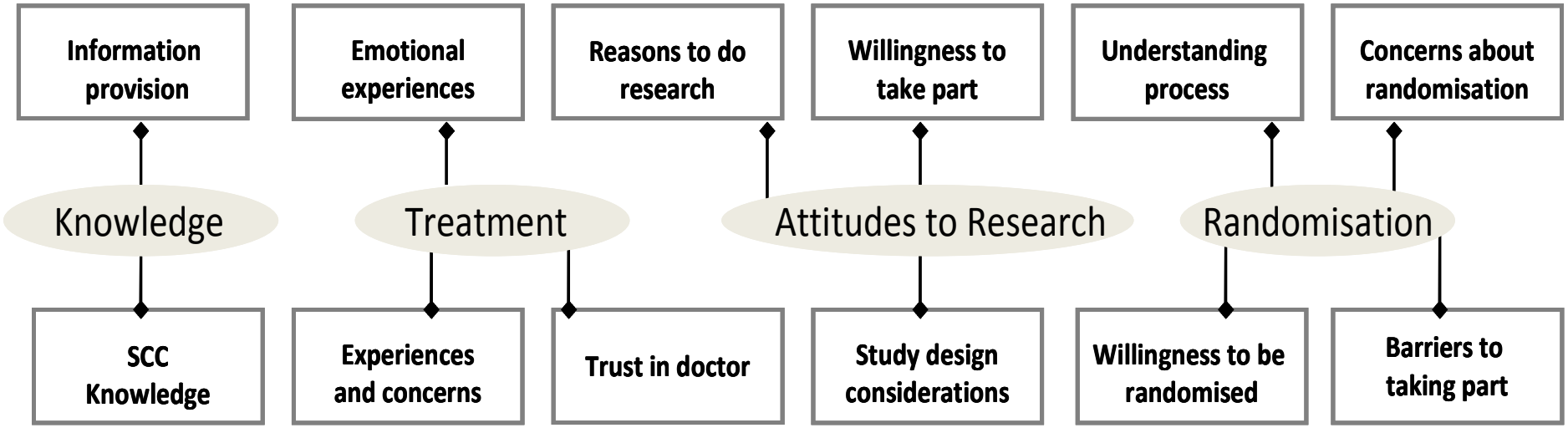


Figure 50. Thematic framework of factors influencing willingness to participate in a two-stage trial of surgery and adjuvant radiotherapy for SCC

8.4 Results

Fifty-nine patients were identified as being potentially eligible for the study, having had surgical excision of an SCC within the specified 12-month period, and were sent letters inviting them to participate. Thirty reply slips (51%) were returned, including one informing the team that the patient had subsequently passed away, so questionnaires were posted to 29 potential participants. Completed questionnaires were returned for 24 participants (83%).

Nineteen men (79%) and five women (21%), with a mean age of 73 years (SD 9), took part in the study. Three-quarters (n=18) of participants were retired, and the remainder were either in full or part-time employment (n=3 participants), self-employed (n=1), or not working due to ill health (n=2). Educational status varied among respondents, with seven (29%) having professional and/or postgraduate qualifications, two (8%) holding a university undergraduate degree, two (8%) having 'A' levels, three (13%) having 'O' levels or equivalent, one (4%) having a School Certificate, 8 (33%) having no formal qualifications, and one (4%) not specifying highest educational attainment.

A total of seven participants also agreed to take part in the focus group (6 men, 1 woman), with a mean age of 70 years (SD 9).

The thematic map was organised according to four overarching themes:

- Knowledge of the condition
- Experiences of treatment
- Attitudes towards research
- Attitudes towards randomisation

8.4.1. Patient knowledge of the condition

Two main areas of knowledge of SCC were identified during the focus group discussion:

- Knowledge of SCC itself, including existing knowledge of causes, risk factors and prognosis
- Information resources used to get information, their adequacy and requirements for provision of information resources for the proposed trial.

Knowledge of SCC

Overall participants in the focus group did not feel well informed about their condition, even though some of them had received treatment for multiple skin cancers. There was little pre-existing knowledge of SCC prior to diagnosis, with some participants previously never having heard of it as a discrete type of skin cancer. Several participants recognised sun exposure as a major risk factor, and there was some speculation that the reason that males are more commonly affected than women may be due to females using sun protection measures more than men.

> **Participant 1 (Male, 62 years)**: "*.. the reason that there's more men here, that they get it more than women. Is it because women wear a lot of make-up on their faces*"

> **Participant 2 (Male, 79 years)**: "*Presumably women are more eager to use the suncreams. I'm thinking of my young daughter and wife, is that they're all very keen to protect their skin whereas men don't seem to bother as much"*

Most participants had at some time attempted to rationalise why they had developed the cancer. Exposure of a cut to aluminium and wire, exposure to grinding dust, radiation treatment, a specific sunburn event, and long-term medication use were cited as potential causes of individual skin cancers. Knowledge of prognosis was variable with some participants not being aware that some SCCs can recur or that there is an increased risk of developing new skin cancers elsewhere. The more 'experienced' skin cancer patients, who had a history of more than one skin cancer, felt quite confident that they would know how to recognise a new skin cancer.

Information provision

Although participants generally had access to information leaflets which were given to them in clinic explaining the condition and its treatment, some could not remember much about them, whilst others found the leaflets were quite useful and interesting. However, there was general agreement that they could have been much better informed about SCC. Some felt that they had been given the leaflets and told to go away and read them, but would like to have had more explanation from the clinicians treating them, although there was acknowledgement of the workload and time constraints of the medical staff and potential to compromise time to treatment, which was a concern to participants.

> **Participant 1 (Male, 62 years)**: *"I got just a leaflet… They never explained. They said 'Take that, read that'. I suppose they were busy doing other things."*
>
> **Facilitator**: *'It sounds like the doctors could talk to you a bit more?'*
>
> **Participant 1 (Male, 62 years)**: *"Yeah, I think so. Especially those that are performing surgery on you or putting you under the knife."*
>
> **Participant 5 (Female, 64 years):** *"That's going to eat into the time they've got and we've said we want quicker treatment."*

The internet was another source of information used by those with access to learn more about their condition, and for some was the main source of information. This was done independently and they had not been recommended particular sites by the clinicians.

Another potential source of information was the skin cancer specialist nurse, and although some participants had been given details of this service during their treatment, none had actually accessed the facility after treatment. One participant also admitted that they were attending the focus group as they felt very poorly informed and were hoping to learn more about SCC from the session.

Participants indicated in the discussion that if they were invited to take part in the proposed RCT, they would like to have a choice of formats through which participant information is provided. It was felt that a website dedicated to the trial would be useful, with details of the trial itself and the research team, with the proviso that any written information, either web-based or in leaflet form, should be easy to understand and the language not too technical. Some participants expressed that they would also want to a face-to-face discussion about the trial, although the concern about taking up too much of the clinician's time was again raised. There was general agreement that access to either a member of the research team or a specialist nurse in order to discuss the trial itself or their own clinical care would be satisfactory and would lessen the burden on the clinician.

8.4.2. Experiences of treatment

Three areas were identified regarding treatment experiences:

- Experiences and concerns about diagnosis, referral and treatment
- Emotional experience
- Trust in the clinicians.

Experiences and concerns about diagnosis, referral and treatment

Although all participants had experienced surgical excision of their skin cancer, there was some variation in their overall experiences and satisfaction with the service. This was most evident with initial diagnosis and referral, where delayed diagnosis by their GP was reported by a couple of participants, which resulted in late referral and the feeling of mistreatment of the condition:

> **Participant 2 (Male, 79 years)**: "*The delays for me were treatment by the doctor [GP], who I felt was mistreating me and I complained and finally convinced a senior doctor that I had to be referred to dermatology.*"

> **Questionnaire respondent 7 (Male, 60 years): "***My main concern was with the identification of the SCC as this was not identified by my GP and it was several weeks before I was referred to hospital and the appropriate action taken. By the time it was dealt with the wound had grown and resulted in two operations to ensure complete removal."*

The concern was raised that GPs should be better educated to recognise skin cancers at an early stage and to make rapid referrals to the specialist secondary care team. Timeliness of treatment was important to participants, and although none expressed dissatisfaction with the two-week wait rule, some were frustrated that the system could not be bypassed if they subsequently developed new skin cancers. The idea of a specialist 'walk-in' treatment day centre attracted some support during the focus group discussion.

Overwhelmingly, the most important treatment outcome for focus group participants was complete removal of their SCC and minimising the chances of it recurring:

> **Participant 2 (Male, 79 years)**: *"When you find out you're going to have an op, all you want to do is make sure the cancer is taken away completely. I don't care how big it is, how deep, but just make sure you get it all away. That was my attitude to surgery."*

The most important outcomes of treatment among the 24 questionnaire respondents were considered to be removal of the cancer (10/24) and minimising the risk of recurrence (11/24); for the remaining three respondents, both outcomes were equally important.

Assurance that the cancer was removed was of greater importance than the size of the surgical wound itself; nevertheless, concerns were expressed about donor skin graft sites which may prove to be more problematic than the recipient site.

Emotional experience

Anxiety, fear and the need for reassurance that the SCC has been treated adequately were all experienced by participants, indicating that SCC is a condition that is viewed as being as serious as other forms of cancer and not merely a trivial inconvenience to those affected by it:

> **Participant 1 (Male, 62 years):** *"When you hear that 'c' word, you naturally assume the worst, whether it's a small cancer or a big cancer, you know, you naturally assume the worst and, I can't think of anything to say – I want to be on this earth as long as possible.*
>
> *…Anxiety, fear, I experienced all that. When they told me I thought my world had collapsed.*
>
> *…But the fear and anxiety when you're waiting to have to go and have it done was horrible, I wouldn't want anybody to go through that. I thought my world was coming to an end."*

Trust in the clinicians

The concept of trust in the treating physician underpinned much of the discussion in the focus group. Implicit faith in the knowledge and skills of the specialist was voiced by some of the participants, with unquestioning acceptance that the treatment they were receiving was in their best interest:

> **Participant 1 (Male, 62 years):** *"I trust the doctor; I trust doctors because that's their job you know. I asked the surgeon "Did you get it out?" and he says "I'm doing them every day, I think I got it all, I've cut more of it away but I think I got it all out." So I trust him….So I believe, I believe in my surgeon, and my life was in his hands."*
>
> **Participant 4 (Male, 81 years):** *"I mean, you just go and he said 'We'll have to cut it out' and you just say 'Well, all right, just get on with it.' I can't tell them what to do. You just trust them."*

On the other hand, some challenged the belief that the surgeon could confidently say that all the cancerous tissue had been removed.

> **Participant 1 (Male, 62 years):** *"The surgeon knows; he's doing them all them every so when he cuts you open he can see roughly, I'm sure he can see, roughly what's there and what he can get out'"*
>
> **Participant 3 (Male, 67 years):** *"I'd be interested to know the answer to that – can he? …Can the surgeon tell when he's chopping away?"*
>
> **Participant 2 (Male, 79 years):** *"No, I don't think he can."*

Having confidence in the treating physician as a pre-requisite to participating in the proposed trial was raised in the questionnaire responses:

> **Questionnaire respondent 28 (Male, 84 years):** *"I would want to have faith in the surgeon/consultant giving the advice and/or operating."*

Providing information to potential participants about the team involved in the trial may therefore be an important strategy to increase trust in those who are going to be administering the treatment arms, thereby encouraging participation.

8.4.3. Attitudes to Research

Four main areas were identified relating to attitudes towards research:

- Reasons for participating in research
- Study design considerations
- Willingness to participate in the proposed RCT
- Barriers to participating in clinical research.

Reasons for participating in research

During the focus group, both personal and more general reasons for taking part in clinical research were discussed. There was a general feeling that clinical research is important in this country. An altruistic sense of giving some

benefit to others and giving something back for treatment received were common themes:

> **Participant 1 (Male, 62years)**: "*I love the thought of helping others if possible"*
>
> **Participant 3 (Male, 67 years)**: *"As for research, I'd be delighted to give something back to the Treatment Centre; they've treated me so well…."*
>
> **Participant 6 (Male, 80 years)**: *"I'm willing to go the extra yard to help others"*
>
> **Participant 2 (Male, 79 years)**: *"Any kind of research is for the benefit of us all, not just ourselves here but for everybody and it is quite important."*

The idea was also expressed that in addition to helping others, discovering more about a disease and advancing treatment, the participant themselves may also benefit from taking part in research:

> **Questionnaire respondent 9 (Male, 62 years)**: "*As I believe skin cancer will return to me, I would like to be involved in any research"*

Study design considerations

The nature of the interventions in the arms of an RCT was considered to be an important factor which may influence the decision about whether or not to participate. Further to discussion about trials involving surgery and those involving new drugs, participants generally felt more comfortable with the idea of taking part in surgical trials:

> **Participant 3 (Male, 67 years)**: *"I suppose there is a history, not necessarily in this area, but other researchers, where they have gone ahead and introduced drugs which have later on proved to be not quite what they thought. I suppose thalidomide is a name that comes to*

mind, but perhaps more drugs than – I think here we're talking more surgery."

Participant 5 (Female, 64 years): *'…I think it comes from the things you hear on the news – how somebody died I don't know how many years ago from taking a tablet from research. So yeah, I would definitely be more comfortable with surgery'*

Some participants were less sceptical than others about taking part in drug trials; although the idea was expressed that wariness about taking part in such trials may be tempered if they were terminally ill:

Participant 5 (Female, 64 years): "*If I was terminally ill I would take anything; if it didn't help me perhaps it would help someone else in the future, but yeah, if I was terminally ill that might be different."*

The idea that participation in a clinical trial may result in getting a new treatment or in closer monitoring of their condition had been considered as an attractive reason to take part, and some agreed that presentation of the trial in such a way may increase their willingness to participate, although this was not an issue for everyone.

Willingness to participate in the proposed RCT

There was general agreement in the focus group discussion that, in principle, participation in the first surgical stage of the proposed trial would not be overly concerning, although reservations were expressed about having larger margins for SCCs located on the face, (particularly in younger or female patients), or periorificially, where function could be compromised.

Participant 5 (Female, 64 years): "*I think it could depend on who you are, how old you are, where it is as to how much …. If you're a young woman you might prefer as little as possible."*

Participant 2 (Male, 79 years): *"I think the site of this is important too. Obviously if it's on the face you wouldn't be volunteering for 10mm if it wasn't necessary, and it hasn't been proved necessary yet'"*

Participant 3 (Male, 67years): *"I think if it's near the eye or any other opening, if you think it's going to affect the working of the eye by pulling the nerves or damaging the nerves or whatever then I would think a bit more carefully about this… but if it's on your shoulder or whatever, then you'd take a bit more."*

Participant 1 (Male, 62 years): *"I'd go for that. If it's on your face then go for as little as possible…"*

Problematic skin grafts following surgery had been experienced by some of the focus group participants, and were discussed as a factor which would impact negatively on willingness to take part in a trial involving larger excision margins.

Willingness to participate in the second stage of the proposed RCT, in which adjuvant radiotherapy after surgical excision will be compared with no adjuvant radiotherapy, was more reserved. Several participants both in the focus group and questionnaire respondents, expressed fear over having additional radiotherapy, with possible side effects and '*doubts as to whether radiotherapy really works – too random kill or cure*' being raised as reasons for reluctance to participate.

One participant who had previously had radiotherapy as part of a trial was very suspicious that his skin cancer had been caused by the radiotherapy, and has subsequently been left '*very frightened of all forms of it*'. The psychological impact of being in the adjuvant radiotherapy arm of the proposed RCT was also raised as an issue in the focus group discussion, with the suggestion that the disease would be perceived as being more serious by the participant:

Participant 5 (Female, 64 years): *"I think it would definitely take over your life and it also becomes in your head more serious…up to 6 weeks, you know, in your head, it's more serious."*

Barriers to participation

Other than the specific reasons indicated above regarding willingness to take part in the individual stages of the RCT, more general barriers to recruitment were identified in the focus group and questionnaires. Some of these were age-related: extra visits to hospital; feeling worn-out after hospital visits; lack of concentration; concern over the future; and pre-existing deafness were some potential barriers which were of concern to individuals. The inconvenience of possible extra hospital visits in terms of time commitments, transport, travel and parking expenses was an important consideration for some. The retired focus group participants discussed that time may less of an issue for them but did feel that parking and travel expenses should be reimbursed for participants.

8.4.4. Attitudes to randomisation

Three areas relating to randomisation in RCTs were identified:

- Understanding of the randomisation process
- Concerns about randomisation
- Hypothetical willingness to be randomised in the proposed RCT.

Understanding randomisation

The concept of randomisation was an area of confusion, with some focus group participants never having heard of the process and others having vague ideas about why and how randomisation is done.

Participant 1 (Male, 62 years): "*Is that when they pick from all angles, all walks of life..?"*

Participant 2 (Male, 79 years): *"I would imagine it's a bit like Ernie that picks a number out and that's the one you get."*

Participant 7 (Male, 60 years): *"…I think sometimes you use a control, so sometimes you give a placebo where you get no treatment at all."*

Concerns about randomisation

Concerns about randomisation raised by respondents to the questionnaire (who had been given a brief outline of the randomisation process in the participant information sheet), related to misunderstanding of the purpose of randomisation, lack of equipoise and the perceived threat to the optimal care of the patient.

Questionnaire respondent 9 (Male, 62 years): *"People might meet this situation as a life-or-death predicament and would therefore want the optimal treatment and not be randomised so they take pot-luck – whether or not radiotherapy is offered when it is something they might need – not to be withheld therefore."*

Questionnaire respondent 10 (Female, 64 years): *"Fear of not getting the treatment which is most effective for their SCC"*

Questionnaire respondent 12 (Male, 76 years): *"My hesitation arises out of the obvious concern that the randomised treatment selection will not be the optimum treatment for me….although I appreciate that the study is in fact an attempt to establish optimisation."*

Interestingly, one participant felt that the uncertainty of the effectiveness of the different treatment arms in the RCT would actually discourage them from wanting to take part.

Further to explanation of the randomisation process in the focus group, the general consensus was that randomisation should not be seen as threat to the best care of the participant, although there was still some concern about not getting the usual treatment for a condition and about delays to treatment which may be incurred during the research process.

Participant 5 (Female, 64 years): *"Maybe if I wasn't getting something that somebody normally got for what I have, so that I was actually not getting it, then I think..mm, is this the right thing to do?"*

Participant 6 (Male, 80 years): *"If you had a very fast growing cancer like my wife, when you could almost sit at the table and watch it grow, then you'd want it going into fairly quickly."*

Hypothetical willingness to be randomised into proposed trial

Questionnaire participants were asked whether they would hypothetically be prepared to be randomised into one or both stages of the proposed trial. Eight of the 24 (33%) questionnaire respondents indicated that they would definitely be willing to be randomised to both stages of the proposed RCT, and a further 5 (21%) that they would probably be willing to be randomised to both stages. Two participants (8%) said they definitely would not want to randomised to either stage, one (4%) probably would not and eight (33%) were not sure. Two (8%) respondents indicated that they would only want to be randomised for the first surgical stage of the trial, and an additional two (8%) would probably be willing to be randomised to the first stage only. One respondent (4%) indicated willingness to be randomised to the second adjuvant radiotherapy stage only. Therefore, in total, 17 (71%) participants indicated definite or probable hypothetical willingness to be randomised into the first stage of the RCT, and 14 (58%) into the second stage which was not a statistically significant difference (McNemar's test, p=0.37).

Those who were hypothetically willing to be randomised into both stages of the proposed trial were significantly younger than those who were unsure or unwilling (independent samples t-test, mean difference 8.6 years, 95% confidence intervals 1.7 to 15.4, p=0.016). With regard to gender, educational status and employment status, participants did not differ significantly in their willingness to be randomised into both stages of the proposed trial, although the study is unlikely to be sufficiently powered to detect differences (Fisher's test p=1.00, p=0.42 and p=0.60 respectively (Table 40).

Table 40: Distribution of participants by willingness to be randomised to both stages of proposed trial

Factor	Definitely/probably willing (N=13)	Not sure/probably or definitely not willing (N=11)	Total (N=24)	P-value
Age (mean ± SD)	68.5 ± 7.8	77.1 ±8.3	72.5 ± 9.0	**0.016***
Gender:				
Male	10 (53%)	9 (47%)	19	1.00**
Female	3 (60%)	2 (40%)	5	
Educational level:				
School	7 (47%)	8 (53%0	15	0.423**
Higher/professional	6 (67%)	3 (33%)	9	
Employment status:				
Employed	3 (75%)	1 (25%)	4	0.60**
Retired/otherwise not working	10 (50%)	10 (50%)	20	

*- independent samples t-test; ** Fisher's test

Treatment preferences

In response to questions about preference for one treatment arm over the other for each of the stages of the trial, six of those who claimed they would definitely or probably be willing to be randomised into both stages of the trial indicated a strong preference for one of the treatment arms. Four of these respondents favoured a more radical approach, with preference for the larger surgical excision margin and adjuvant radiotherapy.

> **Questionnaire respondent 14 (Male, 68 years)**: *"Sounds to me like a better chance of removing everything"*
>
> **Questionnaire respondent 19 (Male, 86 years)**: "*Gives more chance of removing cancer (10mm margin)"*
>
> **Questionnaire respondent 19 (Male, 86 years)**: "*Again I feel it will help in complete recovery (ART).*"

Cosmetic reasons were given for preference for a smaller margin in the remaining two participants.

Four participants who were definitely or probably willing and one who was definitely not willing to be randomised to the first surgical stage expressed a strong preference for one of the treatment arms (Figure 51). The association between strength of preference and willingness to be randomised was not significant (Fisher's test, p=1.00). Three participants (one of whom was definitely not willing to be randomised, one who definitely was, and one who probably would) expressed a preference for a 10mm margin on the grounds that the wider margin would optimise the chances of removing the cancer. The remaining two participants both expressed a strong preference for a 6mm margin over 10mm for cosmetic reasons, although both were still definitely willing to be randomised into the first surgical stage.

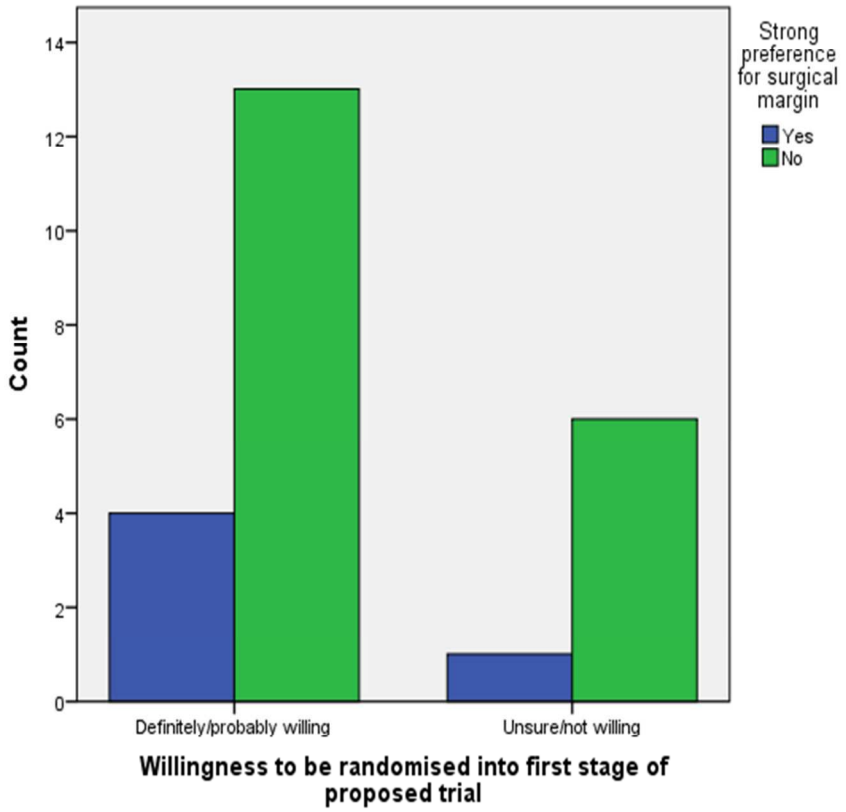


Figure 51: Strength of preference and willingness to be randomised into the first stage

No-one who was definitely willing to be randomised into the second stage of the proposed trial expressed a strong treatment preference, and one person who was definitely not willing to be randomised expressed a strong treatment preference (not to have ART). One other person who was unsure whether they would be prepared to be randomised into the ART stage also expressed a strong preference not to receive ART as they attributed their SCC to previous radiotherapy treatment. Four other participants, three of whom would probably be willing to be randomised into the ART stage and one who probably would not, expressed a strong preference to have ART as they felt they would have a better chance of tumour clearance by receiving ART, particularly if there was nerve involvement. Overall, the relationship between strength of preference and hypothetical willingness to be randomised into the second stage was not statistically significant (Fisher's test, p=0.66) (Figure 52).

Age, gender, employment status, and educational level were not significantly associated with strength of preference for treatment in either of the stages of the proposed trial (Table 41).

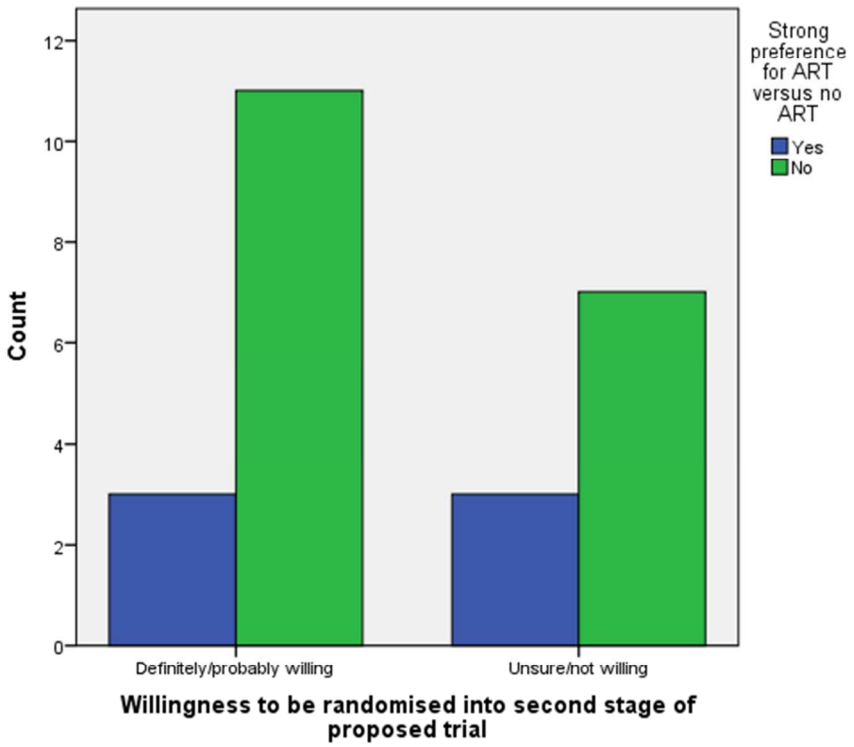


Figure 52: Strength of preference and willingness to be randomised into the second stage

Table 41: Distribution of participants by strength of preference for one treatment arm over the other for each randomisation stage

Factor	Surgical randomisation stage		p-value	ART randomisation stage		p-value	N=24
	Strong preference	No strong preference		Strong preference	No strong preference		
Age in years (mean ± SD)	69.8 ± 6.9	73.2 ± 9.5	0.47*	73.8 ± 7.2	72.0 ± 9.6	0.68*	72.5 ± 9.0
Gender:							
Male	5 (26%)	14 (74%)	0.19**	6 (32%)	13 (68%)	0.20**	19
Female	0 (05)	5 (100%)		0 (0%)	5 (1005)		5
Educational level:							
School	4 (27%)	11 (73%)	0.36**	3 (20%)	12 (80%)	0.40**	15
Higher/professional	1 (11%)	8 (89%)		3 (33%)	6 (67%0		9
Employment status:							
Employed	1 (25%)	3 (75%)	1.00**	1 (25%)	3 (75%)	1.00**	4
Retired/otherwise not working	4 (20%)	16 (80%)		5 (25%)	15 (75%)		20

* independent samples t-test; ** Fisher's test

8.5 Discussion

This feasibility work has identified some previously recognised factors which may influence recruitment into clinical trials generally, but is the first that has specifically addressed recruitment into a trial for cutaneous SCC. By recognising misunderstandings and concerns about clinical research generally, and the specific trial proposed, appropriate strategies can be devised to overcome these and to enhance recruitment.

8.5.1. Patients' knowledge of squamous cell carcinoma

Specific knowledge about cutaneous SCC was generally poor, with confusion about the causes of the condition and its prognosis, even among those who had a history of previous skin cancers. This confirms the findings of two other studies that have assessed the knowledge of patients with skin cancer, although neither of these related specifically to SCC (Bath-Hextall et al., 2013, Wright and Bramwell, 2001). In terms of recruitment into the proposed trial, a lack of patient knowledge about SCC in itself should not be a barrier as potential participants will receive patient information resources providing background information about SCC, including its natural history, the treatments options and possible implications of the different treatment arms.

8.5.2. Provision of information

The way that such information is presented will be key to enhancing the understanding of potential participants. It should be clear, use language that is appropriate to a lay person and available in a choice of formats. The need for the provision of high-quality information, appropriate to the needs of the patient at that point in their diagnosis, and repeated over time, has been highlighted previously (National Institute for Health and Clinical Excellence, 2006) . Receiving a diagnosis of skin cancer induces anxiety and fear in those affected, and the lack of recall of information given at initial diagnosis may be a reflection of the emotional state of the patient at the time (Bath-Hextall et al., 2013). Skin cancer guidance advises that information provided should

therefore be repeated over time, and be available in other formats such as audiotapes of consultations, videos or other specialised materials if appropriate (National Institute for Health and Clinical Excellence, 2006). This was raised as an option that potential participants would like to have.

8.5.3. Timeliness of diagnosis and treatment

There was general recognition of the need for rapid diagnosis and treatment of SCC, and an overwhelming view that the most important outcome of treatment should be to completely remove the tumour and to minimise the risk of it recurring. Although generally not a life-threatening condition, those affected want minimal delays in referral and treatment. Compromised timeliness of treatment caused by the research process itself would therefore not be tolerated by potential participants. However, delays previously experienced by participants in this study were related to diagnosis of SCC rather than the treatment received after referral to the specialist. Current recommendations are that patients with suspected cutaneous SCC should be urgently referred to a specialist and seen within two weeks of referral (National Institute for Health and Clinical Excellence, 2006, National Institute for Health and Clinical Excellence, 2005). Perceived delays in referral by the GP due to misdiagnosis caused frustration and enhanced anxiety for those who had had such an experience and raised concern that some GPs may not be adequately educated to diagnose suspected SCC. The ability of GPs to diagnose skin cancer varies widely (Bedlow et al., 2000, Chen et al., 2001) , and although several studies have evaluated the impact of educational interventions on improving diagnostic accuracy amongst primary healthcare providers, these tend to be isolated interventions and have generally not been rigorously evaluated (Goulart et al., 2011). Educational interventions have been found to be of variable effectiveness (Shariff et al., 2010, Bedlow et al., 2000), and modifying and maintaining clinical practice in the long-term can be challenging (Girgis et al., 1995). Studies addressing educational interventions with outcomes that focus on performance changes are

therefore required, but outside the remit of the current study and the RCT we are proposing.

8.5.4. Drivers to participate in clinical research

Understanding of the clinical research process, and how and why randomisation is done, was lacking among participants in this study. Nonetheless, there was general consensus that clinical research is important and that it helps moves treatment forward. A sense of altruism was identified as a positive driver to participate in research. Additionally, there was some feeling that having a terminal illness as opposed to less advanced disease in an individual may enhance this altruistic attitude. Other studies of willingness to take part in clinical trials in patients with metastatic disease as opposed to primary disease have confirmed this (Catt et al., 2011, Garcea et al., 2005). Conversely, reasons to participate may also be in the self-interest of the individual, based on the belief that the treatment they receive may be an advantage to them personally, and that by helping to move the evidence base forward they may themselves benefit from any advances should they require treatment for the same condition in the future.

8.5.5. Understanding of randomisation

Misunderstanding of the concept of randomisation, or the perceived advantage of one treatment arm over another, may be seen as threats to optimal care and may fuel uncertainty and additional anxiety which may compromise successful trial recruitment. Even though questionnaire respondents in this study had been given information about the nature of the randomisation process and its purpose, uncertainties and concerns about randomisation were evident from their responses, underpinning the need for clear, accurate provision of such information for potential trial participants. However, the idea of randomisation is difficult for lay people to accept, and their interpretation may differ from that of medical professionals, so there may be a need for further discussions with potential recruits in order that they are informed sufficiently to be able to give informed consent (Whitley and Ball, 2002). Furthermore, provision of additional information has been

shown to sway attitudes positively towards participation in those initially dissenting from taking part in cancer trials, and careful in-depth discussion may resolve some of the concerns about randomisation (Jenkins et al., 2010).

8.5.6. Treatment arm preferences

Patient preference for one treatment arm over the other was expressed by some participants in this study. This included some of those who claimed that they would be hypothetically willing to be randomised into one or both stages of the trial, although the perceived benefit of one of the treatment arm is evidently going to influence their final decision whether to take part and risk receiving their non-preferred treatment. The relationship between the strength of preference for one of the treatment arms over the other in each stage of the proposed trial was not found to be statistically significant. However, numbers were small so any statistical inferences need to be interpreted cautiously. Of the two patients who were not willing to be randomised into the ART stage, one commented that they would not like to have radiotherapy at all, and the other that they would be concerned about missing the opportunity to receive a treatment that could be beneficial if they were randomised to the non-ART arm. Other studies have found a strong association between willingness to be randomised into trials and strength of treatment preference, with those expressing a strong preference for a particular treatment being more reluctant to be randomised (Mills et al., 2003, Llewellyn-Thomas et al., 1991, Wragg et al., 2000, Creel et al., 2005). Lack of patient equipoise is a recognised barrier to recruitment (Kaur et al., 2013), and one that will need to be probed and challenged by researchers and clinicians who are presenting the trial and taking part in discussions with potential participants. If potential participants strongly believe that one of the treatment arms is more likely to benefit them, they may be less willing to chance receiving a treatment they perceive to be inferior in the process of randomisation.

8.5.7. Trust in the clinician

Several studies have found that the clinician introducing the trial to potential participants has the greatest influence on their decision to take part or not and that lack of confidence in the doctor will negatively influence this decision (Ross et al., 1999). The role of trust in the knowledge and advice given by the clinician has been seen to be of importance to participants in this study. The level of this trust is therefore likely to have a positive impact on patients' willingness to take part in the proposed trial. On the other hand, some patients may feel that the process of randomisation may compromise the doctor–patient relationship and undermine trust in the doctor, preferring instead for the clinician to make the any treatment decisions for them. Trust as a disincentive to participate in trials has also been reported elsewhere (Dupont and Plummer, 1990). Clinical equipoise in individual clinicians recruiting participants into trials is of fundamental importance to a trial's success and lack of equipoise may be a particular issue in trials involving surgical interventions (McCulloch et al., 2002, Hamilton et al., 2013). Additional training of clinicians consenting participants may therefore be necessary to help overcome this. Another approach would be to run a parallel, non-randomised preference arm alongside the main RCT (McCulloch et al., 2002). A parallel study would, however, generate less robust data than a well-conducted RCT and may impact upon the numbers and types of patients agreeing to take part in the main RCT. For a condition in which outcomes after treatment are relatively rare, and which will require recruitment of a large number of patients in order to enable adequate powering of the RCT, the loss of potential participants to a non-randomised study could impact upon the overall success and usefulness of the main RCT.

8.5.8. Possible barriers to recruitment

General willingness to participate in clinical research may be moderated by factors relating specifically to the trial in question. Regarding the proposed SCC trial, participation in the surgical stage was seen as less of a threat than, for example, taking part in a trial involving a new drug or in a trial in which

there was the possibility of being randomised to a placebo arm, which has been recognised as a disincentive to participate in trials (Locock and Smith, 2011), (Jenkins et al., 2013). Although almost three quarters of participants claimed they would definitely or probably be willing to be randomised into the first surgical stage, the decision about whether to participate or not may be complicated by potential cosmetic implications, particularly for younger, female patients and for SCCs located on the face or in a functionally sensitive area (e.g. around the eye). Overall, hypothetical willingness to be randomised into the second stage of the proposed trial involving adjuvant radiotherapy was less enthusiastic, with 54% claiming definite or probable willingness to be randomised. Concerns about receiving radiation were cited as the major barrier to participation in those who said they would not be willing to be randomised. In contrast, of the participants who did claim to be potentially willing to be randomised, those who expressed a preference for one of the treatment arms said they had a strong preference to receive the adjuvant radiotherapy as they felt there was a better chance of it clearing the cancer. The proportion of potential participants who are hypothetically willing to be randomised is therefore likely to be an overestimate of the actual numbers, which will need to be taken into account when designing the trial. Other patient-related factors were identified as barriers to the proposed trial, and primarily related to participation in the second radiotherapy stage. Some saw the extra hospital visits that would be required as part of the radiotherapy regimen as an inconvenience in terms of time, transport and cost, so the provision of additional costs for reimbursement of trial-incurred expenses should be considered as a strategy to encourage participation. Advanced age, physical frailty, the presence of co-morbidities and uncertainty about the future were also identified as reasons why some people may be reluctant to become involved in research. The results of this feasibility study have indicated that there is a significant difference in the mean ages of those people would theoretically be prepared to be randomised into either stage of the trial, with older people being less willing to take part. Age-related factors are recognised as a significant barrier to recruitment into trials (Townsley et

al., 2005, McMurdo et al., 2011), yet in the proposed trial the population pool from which recruits will be drawn will be largely over the age of 70 years. Exclusion criteria related to comorbid conditions and previous malignancies may therefore need to be modified in the protocol if older and more frail patients are to be included in the research and for the trial results to be externally valid. Extra resources may additionally be required for research personnel to spend time with older participants to explain the protocol and to obtain informed consent.

8.5.9. Strengths and limitations of the study

Evaluation of the understanding and concerns about clinical research generally and the specific trial being developed provides an insight into potential barriers which may affect the willingness to participate in such a trial, and the opportunity to incorporate strategies in the protocol to overcome these barriers.

A limitation of this study is that all participants had previously had surgical treatment of a cutaneous SCC and therefore had more insight and expectations of treatment than people presenting for the first time and invited to participate in the proposed trial. However, as none of them had had adjuvant radiotherapy after surgery, this insight would be less of an issue for the second stage of the proposed trial. Most participants in this study would have regarded their surgical treatment as a 'cure', and this may have influenced their response regarding randomisation into the second stage as none of them received ART during their own treatment. Nevertheless, it is possible that actual trial participants who are eligible to be randomised to receive ART or follow-up alone will have a different perception of ART from this study group, and that faced with the nature of their condition, concerns regarding radiotherapy may be less of a concern. An advantage of having participants with prior treatment experience is that it allows for evaluation of the needs for the provision of information resources, and, given the lack of a patient support group for this condition, has supplied a pool of volunteers who are theoretically willing to review patient materials produced.

People who returned their questionnaires and who took part in the focus group may be more motivated to take part in research generally, so the numbers who declared hypothetical willingness to be randomised may not be a true reflection of the population pool generally and needs to be interpreted with caution. Furthermore, an individual's stated preference in a hypothetical scenario may not be an accurate reflection of what they would actually decide in a real-life situation.

Although more males than females participated in this study, this was not intentional and reflects the demographics of the population that is affected by this condition.

8.5.10. Summary of the main lessons learnt from this study

- Participants generally had poor understanding of SCC even though all had experienced treatment of the condition.
- Understanding of the processes of clinical research and randomisation was poor among participants.
- Overall participants did not regard the proposed RCT as being unfeasible.
- Randomisation to one of the surgical arms in the first stage of the proposed trial was not overly concerning for participants, although willingness to be randomised would depend if their SCC was located in a cosmetically or functionally-sensitive site.
- Generally participants would be more reluctant to be randomised into the adjuvant radiotherapy versus no radiotherapy arm of the second stage of the proposed trial. Concerns about receiving radiation were cited as the main reason for this.
- Potential participants in a future RCT would want information about the trial to be provided in a variety of formats.
- The randomisation process will require thorough explanation, and may require additional time and staff input to ensure that participants are thoroughly cognisant of the process and to optimise their willingness to be randomised.

- The concept of clinical equipoise will need reinforcing in order to overcome trialists' and participants' potential preference for one treatment arm over the other.

8.5.11. Conclusions and Implications for research

This study has allowed evaluation of potential barriers to participating in the proposed skin cancer trial in a population representative of those who would be eligible to take part in the trial itself. Importantly those who participated in this study did not reject the proposed trial as being unfeasible.

Actual numbers who are willing to participate in each stage will not be known until the trial is underway, and the suggestion from this study is that eligible participants are less likely to want to be randomised into the second stage of the trial. The incorporation into the protocol of an initial pilot phase to assess recruitment may therefore be prudent, with an alternative strategy such as a parallel non-randomised arm if participants express a strong preference for one treatment over the other or if recruitment does not reach target.

Understanding the needs and concerns of potential participants will allow the development of appropriate information resources for the trial, which will be of crucial importance to help potential participants make an informed decision about whether or not to take part in the trial.

CHAPTER 9:

THE TRIAL PROPOSAL

9 THE TRIAL PROPOSAL

9.1 Introduction

The trial proposal described in this chapter is the most recent version culminating from the research of this thesis and the multidisciplinary discussions that have been taking place.

As discussed in preceding chapters of this thesis, there has been a lack of research comparing the effectiveness of SCC treatments, and no RCTs that have compared different treatments for the primary, non-metastatic SCCs that are seen most commonly in everyday clinical practice. The work described in this thesis has been at the heart of the development of a trial proposal for what will be the first RCT addressing the treatment of SCCs. In order for this to happen, multidisciplinary collaboration has been essential, and has therefore involved much discussion and debate. As a result, the proposal has evolved considerably from the initial ideas for a clinical trial that emerged from the survey of clinicians in 2010 and which were outlined in chapter 6.

As the discussions evolved, it was felt that a third MMS arm could usefully be added to the first randomisation stage so that comparison of outcomes after surgical excision with the predefined margins and Mohs surgery could be evaluated prospectively; an area which, as described above, remains contentious. However, concerns were raised by some of the surgeons that with technically it is difficult to achieve a clear distinction between 6mm and 10mm margins and that just comparing a surgical margin of 10mm versus MMS to clearance would actually be preferable and yield the most useful data about adequacy of surgical excision and a direct comparison between MMS and standard surgical excision. There has been concurrence regarding the importance of the second-stage of randomisation to ART versus no ART throughout the trial development. This design therefore forms the basis for

the current trial proposal which will be described in section 9.2 of this chapter.

The history of the trial proposal and its context in relationship to the other areas of research in this thesis is represented schematically in Figure 53.

The feasibility work with patients (chapter 8 of this thesis) was instigated during the development stage of the proposed trial to assess the acceptability of proposed trial with potential participants and to identify potential barriers to recruitment which may need to be addressed in the protocol. Although the trial scenario presented to the participants in the feasibility work compared excision margins of 6mm and 10mm rather than wide local excision with MMS, the lessons to be taken from it are still valid. Participants had fewer concerns regarding the surgical stage than the second adjuvant radiotherapy stage, and it is at this stage where recruitment challenges are most likely to be encountered. Participants' information requirements and the need for careful presentation of the proposed trial so that clinical equipoise is maintained, particularly in relation to ART, remain the same, regardless of the exact details of the surgical intervention. One of the most important lessons from the feasibility work was that understanding of the randomisation process in the group representative of potential participants was poor, and this issue will require particular explanation in any SCC trial, and may require additional resources to be inputted.

9.2 The current trial proposal

The remainder of this chapter will focus on the trial proposal that has evolved through this research and the multidisciplinary collaboration as described above.

9.2.1. Aims and Objectives

- To assess whether there is a difference in the rate and timing of locoregional relapse between patients with high-risk T2 SCCs which have been excised with a 10mm surgical margin, and those treated with Mohs micrographic surgery.
- To assess whether there is a difference in the rate and timing of locoregional relapse in patients who are treated with post-operative radiotherapy, and those who are treated by excision with a 10mm margin or Mohs micrographic surgery alone.
- To develop a prognostic model for treatment of patients with high-risk SCC.

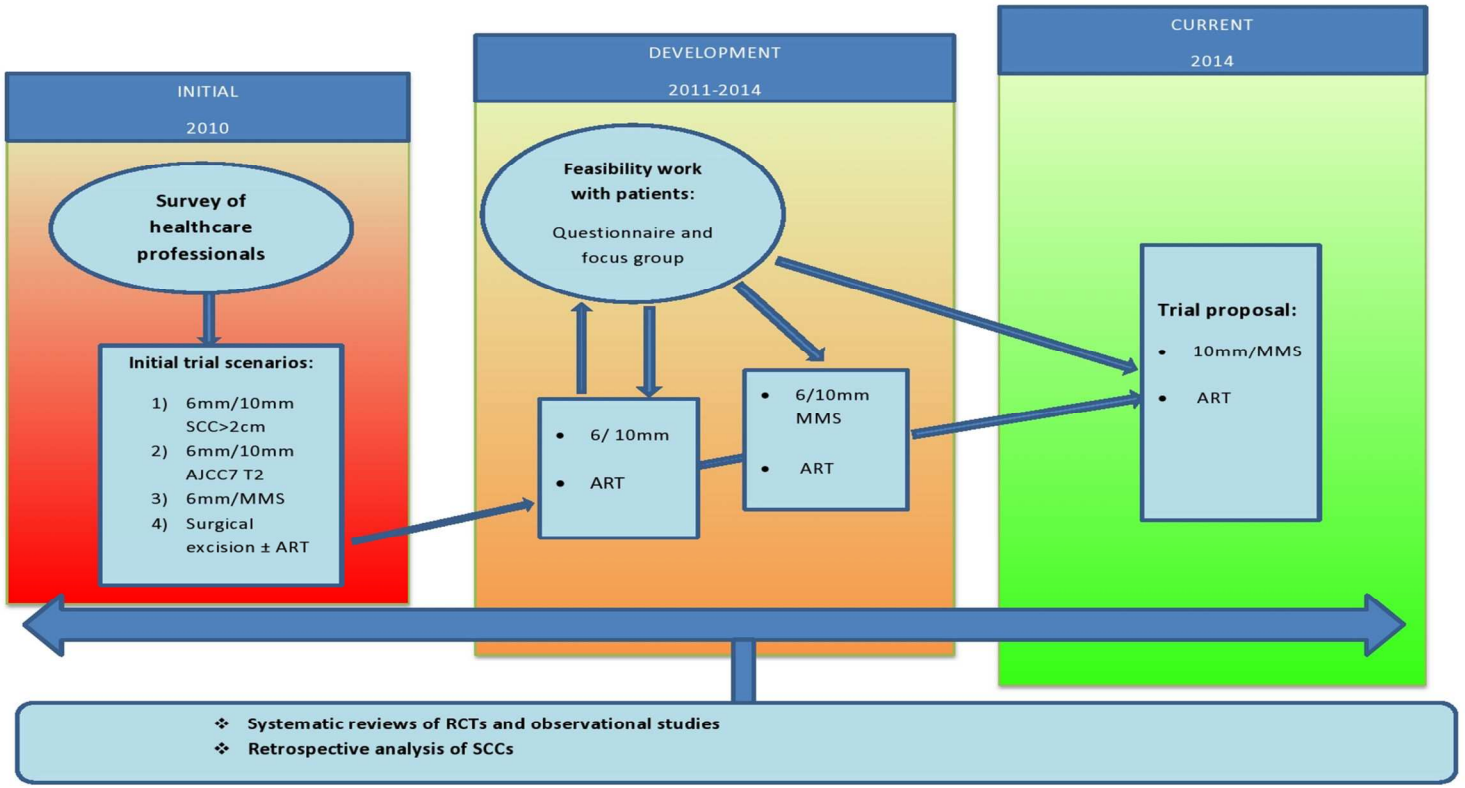


Figure 53: Development of trial proposal

9.2.2. Trial Design

The proposed trial is a pragmatic, multicentre, two-stage, non-blinded RCT comparing excision with a 10mm surgical margin with Mohs micrographic surgery, and comparing adjuvant radiotherapy after surgery with no adjuvant radiotherapy (Figure 54). The primary outcome will be time-to-first locoregional recurrence within 3 years of treatment, although participants will be followed up for 5 years after the end of treatment for assessment of late outcomes associated with radiotherapy.

Due to the nature of the interventions, it will not be possible to mask participants and principal investigators to the treatment allocated, and only partially possible mask outcome assessors. However, the allocation sequence will be concealed from participants and investigators so that they are not aware of the treatment group into which patients will be put prior to randomisation.

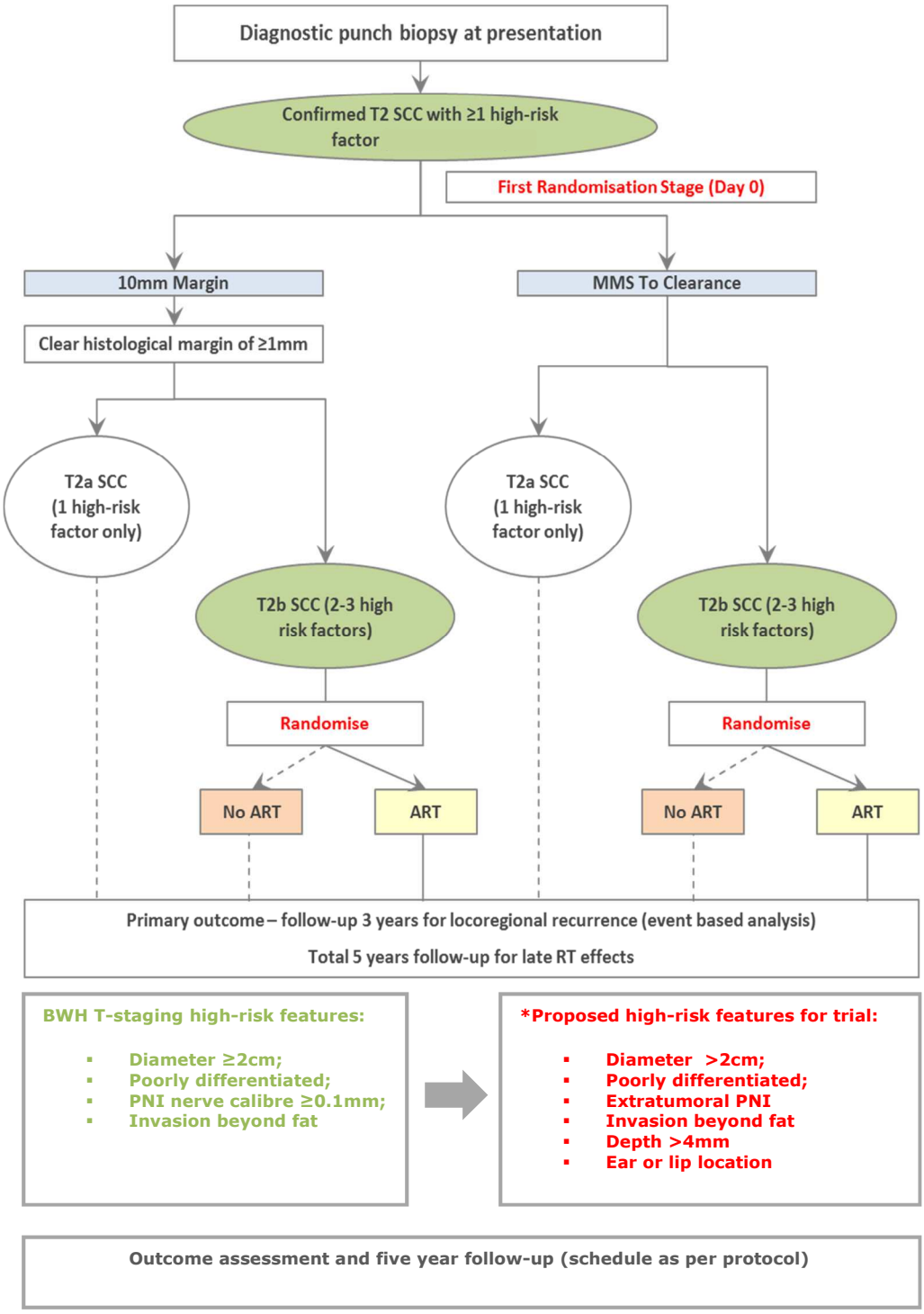


Figure 54: Outline of proposed SCC trial

9.2.3. Setting and Target Population

Target population

Participants will be adults (at least 18 years of age) with primary invasive, non-metastatic high-risk SCC of the skin. The tumour staging criteria described in Table 22 and which are based on the Brigham and Women's Hospital (BWH) proposed criteria(Karia et al., 2013) will be used to identify patients eligible for entry into the trial. Patients having a T2 SCC with at least one risk factor (tumour diameter >2cm, poorly differentiated, perineural invasion, invasion beyond subcutaneous fat >4mm deep, ear or lip location) will be eligible to be randomised into the first surgical stage of the trial. Only patients randomised during the first stage of the trial, and who have 2 or 3 of the above risk factors (i.e. T2b SCCs) will be eligible to be randomised into the second radiotherapy versus no radiotherapy stage of the trial. Therefore, all participants will take part in the first stage of the trial, and patients who have not been randomised in the first stage will not be eligible to participate.

Setting

Recruitment and delivery of the interventions will be provided in secondary care, with identification of potential participants by the skin cancer MDT. The trial will be multi-centre. Site selection will be based upon the availability of a dermatologist or plastic surgeon who is willing to be the Principal Investigator (PI) for the site; the availability of a Clinical Oncology service that can administer the adjuvant radiotherapy intervention; and proven track record of recruiting into other clinical trials.

9.2.4. Eligibility

Inclusion criteria – first stage (10mm excision versus Mohs):

- Patients with a diagnosis of primary, invasive, non-metastatic cutaneous SCC confirmed on diagnostic biopsy.

- The SCC is staged as T2 and has at least one high-risk factor, based upon the staging criteria outlined in section 7.2.1
- A 10mm surgical margin is achievable at the site of the eligible SCC
- The patient is able and willing to give informed consent

Exclusion criteria – first stage:

- Recurrent, previously treated SCC
- Surgery contra-indicated (e.g. Coagulopathy)
- Pregnant or lactating women

Inclusion criteria – second stage (ART versus no ART)

- The patient was randomised to excision with a 10mm margin or Mohs in the first stage of the trial.
- The SCC is staged as T2b and has 2 or 3 high-risk factors, based on the staging criteria outlined.
- The patient is able and willing to give informed consent.

Exclusion criteria – second stage:

- The patient was not randomised to one of the surgical arms in the first stage of the trial.
- History of prior radiotherapy for skin cancer or other conditions
- Radiotherapy contra-indicated – location on back of hand or lower leg

Only one eligible SCC per patient will be randomised. If there is more than one eligible SCC identified, tumours located on the head and neck area will be selected in preference to those located on the trunk. When the is more than one eligible SCC on the head and neck, the SCC that is of greatest concern to

the patient will be chosen, with selection of the largest eligible SCC if the patient has no preference.

9.2.5. Randomisation and blinding

The randomisation schedule will be generated by computer using a randomly varying block size and will be generated and held by the Clinical Trials Unit administering the trial. The trial administrator will carry out the randomisation via a web-based system and alert the surgeon as to which group they are in. The second stage of randomisation will take place after surgical excision and when histology is known in order to identify those SCCs meeting the additional layer of eligibility criteria. Only excised SCCs with histological confirmation of clearance of ≥1mm from the peripheral margin and fascial plane deeper than the level of invasion for deep margin will be eligible for randomisation.

There will be no blinding of participants or principal investigators throughout the trial. Assessors of photographs of cosmetic appearance will be blinded as to participants' identity, interventions received and time since treatment.

9.2.6. Interventions

Surgery

In the first stage of the trial, the intervention will be standard surgical excision with either a 10mm margin of normal-looking skin around the SCC, or Mohs surgery to microscopic clearance of tumour. At presentation, all potentially eligible SCCs will have a diagnostic biopsy. SCCs with at least one high-risk factor (T2) will be eligible to be entered into the trial. Delivery of the Mohs micrographic surgery will be by a consultant dermatologist or plastic surgeon who has undergone a period of additional training in the technique.

Adjuvant Radiotherapy

Adjuvant radiotherapy will be administered by a Clinical Oncologist. The exact regimen has yet to be finalised, but the total recommended dose is 50-60 Gy in daily fractions over the course of four to six weeks and should be given

within 12 weeks of surgical excision. The treated area will include a pre-defined margin of normal looking skin.

The follow-up of participants who receive only surgery and those who also have adjuvant radiotherapy will be identical.

9.2.7. Outcome Measures

Primary outcomes

Primary outcome will be loco-regional recurrence from initial randomisation up to 3 years after treatment. A standard definition of local recurrence will be drawn up to distinguish it from metachronous (new primary) tumours.

Secondary outcomes

The secondary outcomes will be as follows:

- Distant metastases within 3 years of initial randomisation
- Tumour-related death within 3 years of initial randomisation
- Overall disease-free survival (time from randomisation to death from any cause)
- Completeness of surgical excision by measurement of histologically clear margin
- Number of Mohs layers required to clearance of tumour
- Quality of Life (QoL) at baseline, and at each follow-up consultation after completion of treatment. The tool for assessing QoL will be the Skin Cancer Index (Rhee et al., 2006) which is a validated disease-specific tool for patients with NMSC
- Cosmetic appearance of treated area assessed photographically at baseline (post- surgery but before radiotherapy if applicable), and 2 and 5 years post-treatment, by three assessors blinded to participant identity, treatment allocation and year of follow-up

- Adverse events data will be collected from all participants
- Within-trial cost analysis from an NHS perspective

9.2.8. Study Schedule and data collection

Screening for the first stage of the trial will take place upon identification of a high-risk SCC as defined in the trial protocol. This will either be on the initial visit to the Skin Cancer clinic after referral from primary care, or, for SCCs only identified as being high-risk after histology results are available and therefore eligible for randomisation, on the first clinic visit after initial surgery. Randomisation into the second stage will take place when full histological classification after surgery is available which will allow for identification of the highest-risk SCCs as defined in the protocol. Participants potentially eligible for randomisation will be discussed in the skin cancer MDT. Participants randomised to receive adjuvant radiotherapy will be treated no more than 12 weeks after their initial surgery.

Participants will be followed up on a 3-monthly basis until first recurrence, or for 3 years after initial randomisation, with a final assessment at 5 years to allow for assessment of late outcomes associated with radiotherapy. As this is a pragmatic trial, there will be a window of flexibility for the 3-monthly visits. Participants will be given information sheets advising them how to self-examine the treated area, local skin and lymph nodes, and will have access to the research team between clinic visits should they have concerns about recurrences or new tumours.

Histological confirmation of suspected relapses should be sought where possible. Where histology is not readily obtainable, radiological or photographic evidence should be recorded of the relapse.

Management of relapses will be at the discretion of the treating clinician in discussion with the SSMDT. Management of distant metastases may involve

the enrolment of the patient in other clinical trials appropriate to that scenario.

The proposed study schedule is outlined in Table 42.

Table 42: Proposed provisional schedule of study delivery and data collection

	Identification high-risk SCC	D0(a)	Within 2 weeks	1st post-surgery visit/Identification highest risk SCCs	2-12 weeks post surgery	FOLLOW-UP as per protocol up to 5 years	5 years
Informed consent and counselling (a)	✓						
Randomisation to 1st stage (surgical)		✓					
Surgical intervention			✓				
Outcome measurement – margin clearance/ number of Mohs layers			✓				
Baseline QoL				✓			
Baseline photography, clinician and participant rating for cosmetic appearance assessment				✓			
Informed consent and counselling (b) if applicable				✓			
Randomisation to second stage if applicable (ART)				✓			
ART intervention					✓		
Outcome assessment (time to loco-regional recurrence, distant metastases, SCC related death						✓	
QoL assessment						✓ (6 months, 2 years)	
Photographic, clinician and participant rating for cosmetic outcome assessment						✓ (2 years)	✓
Overall survival							✓

9.2.9. Health Economics

An economic evaluation will be conducted alongside the trial and will be incorporated into the protocol. A health economist with experience of cost analysis will be on the Trial Development Team.

In terms of cost-effectiveness of MMS compared with standard surgical incision, the current evidence is conflicting. Surgical excision may be perceived as the cheaper option as it does not involve special training, multiple procedures over the course of up to a day, and expenditure setting up and running a MMS service. However, if there actually are significantly fewer recurrences after MMS, which as discussed above has not conclusively been shown to be the case for SCC, then the cost-savings may be offset by the costs of treating recurrences. Cost-effectiveness studies from the United States suggest that MMS is comparable with, or even less expensive than standard excision. In 1998 a cost-analysis showed that the cost of MMS was $1243 versus $1167 for office-based surgical excision with a permanent section margin control and $1400 for surgical excision with a frozen section margin control (Cook and Zitelli, 1998). More recent studies have found MMS to be between 12% and 33% less costly than surgical excision, depending upon the type of margin control and the setting (office-based or ambulatory surgical centre, which was associated with increased cost) (Tierney and Hanke, 2009, Ravitskiy et al., 2012). However, another study from the United States demonstrated that overall MMS had the highest fees, even when controlling for factors such as tumour size and H-zone location, and attributed the difference to the fact that MMS is often done in areas requiring complex closure for repair (Wilson et al., 2012). The results of costing studies in the United States may not be readily extrapolated to other countries due to differences in the general set-up of healthcare systems and the way in which reimbursement are calculated. A Dutch cost-analysis which was done as part of the RCT of MMS versus surgical excision for facial BCCs reported that MMS costs were significantly greater than surgical excision for treating both

primary and recurrent BCC, and concluded that it was not currently cost-effective to introduce widescale MMS (Essers et al., 2006). However, final analysis when 5 year follow-up data were available, found that an incremental cost-effectiveness ratio (ICER) that was comparable with the cost of two Mohs procedures (initial treatment and treatment of a recurrence), made MMS a potentially cost-effective treatment for recurrent BCC, but not for primary BCC where there was no significant difference in recurrence after MMS and surgical excision (Mosterd et al., 2008).

Thus, a cost-effectiveness analysis would be an important feature of any trial comparing MMS with surgical excision for SCC, and would be one factor to consider when making evidence-based decisions regarding the appropriate treatment of particular SCC if both techniques are otherwise comparable in terms of their effectiveness.

No cost-effectiveness studies have specifically evaluated adjuvant radiotherapy in the treatment of NMSC. One study from the United States, which included all types of NMSC, reported that at $1303 the total cost of treatment per patient for radiotherapy (not specifically ART) was more than five times higher than the cost of surgical excision ($239) and approximately one and a half times more than MMS ($899) (Joseph et al., 2001). Therefore, given the absence of any relevant data pertinent to the UK, a cost-effectiveness evaluation will again be an important component of any trial in which ART is included as a comparator.

9.2.10. Statistical Analysis and Sample Size

Due to the factorial component of this trial proposal, the sample size calculation will be done by an experienced statistician who has expertise in the area and who will be a member of the Trial Development team. An approximate sample size calculation is given below based upon the data obtained and discussed earlier in this thesis (chapters 4 and 7). It will be necessary to recruit a large number of patients if the trial is to be adequately

powered to detect if there is a clinically significant difference between the treatment arms as the frequency of recurrence has been shown to be low in both the systematic review (chapter 4) and in the case series of SCCs treated in Nottingham (chapter 7).

The purpose of the RCT is to determine the main effects of the interventions under consideration, therefore, the main hypotheses focuses on the two primary questions. The researchers do not wish to answer which of the four possible combinations is the most effective, thus the effect of the interaction is of marginal interest. The main hypotheses is addressed by assuming that ART will be equally as effective irrespective of whether the patients received surgery or MMS in the preceding randomisation phase. This assumption is likely to be valid since the requirement for a patient to proceed to the second phase of the randomisation is based on whether there was an absence of incomplete excision.

The failure rates for local and regional recurrence for surgery (5.4% and 4.4%, respectively) and MMS (3% and 4.2%, respectively) as determined by the pooled analyses in Chapter 4 cannot be used directly in the sample size calculation for the first phase of the trial as they include low and high risk patients. Additionally, the data provided in the included studies did not allow for estimations to be determined for just high risk patients. Therefore, using additional failure rate data on high risk patients from Chapter 7 (BWH classification T2b), the following range of likely failure rates were used in the sample size calculations (Table 43):

Table 43: Estimated outcomes for each intervention (range)

Intervention	Local recurrence, (range)	Regional recurrence, (range)
Surgery	20% (15%, 25%)	12% (10%, 14%)
MMS	15% (10%, 20%)	8% (6%, 10%)
ART	15% (10%, 20%)	8% (6%, 10%)

The failure rates for local and regional recurrence for adjuvant radiotherapy (ART) following surgery as determined by the pooled analyses in Chapter 4 were reported separately for lesions with and without PNI, with average pooled failure rates of 15% for local recurrence and 8% for regional recurrence. The above table shows the likely failure rates used in the sample size calculations.

Additionally, from Chapter 4, there was incomplete excision in 8.8% of surgery patients, although definition of adequacy of excision varied between the included studies, and from Chapter 7 there was incomplete excision in 14% of surgery patients. Therefore, for the RCT we assumed that incomplete excision would occur in 14% of surgical patients; thus 86% of patients with T2b SCCs who were randomised in the first phase to have surgical excision would be eligible for randomisation in the second phase of the study.

Using the data above, sample sizes for the second phase of the study were calculated using chi-squared tests for two proportions assuming 5% significance level (not allowing for multiple testing) and 2.5% significance (allowing for multiple testing) at 80% and 90% power, assuming that ART was more effective than no ART:

ART failure rate	**No ART failure rate**	**Power of study**	**Sample size in each group (5% significance level)**	**Sample size in each group (2.5% significance level)**
Local recurrence				
15%	**20%**	**80%**	**945**	**1137**
15%	20%	90%	1252	1471
15%	25%	80%	270	323
15%	25%	90%	354	415
10%	15%	80%	726	870
10%	15%	90%	957	1124
10%	20%	80%	219	261
10%	20%	90%	286	334
20%	25%	80%	1134	1365
20%	25%	90%	1504	1769
Regional recurrence				
8%	**12%**	**80%**	**932**	**1118**
8%	12%	90%	1230	1444
8%	14%	80%	459	549
8%	14%	90%	603	706
6%	10%	80%	771	923
6%	10%	90%	1014	1190
6%	12%	80%	389	464
6%	12%	90%	509	596
10%	14%	80%	1085	1303
10%	14%	90%	1435	1686

A two sample continuity corrected chi-squared test with a 2.5% significance level (to account for multiple testing) based on an odds ratio of 1.42 for local recurrence (15% ART versus 20% no ART) will have 80% power when the sample size is 2274 (1137 per group) or 90% power when a sample size of 2942 (1471 per group) is used. These sample sizes will also be sufficient to detect an odds ratios of 1.57 for regional recurrence (8% ART versus 12% no ART).

As only T2b SCC are eligible for the second phase of the trial, the sample sizes above are also applicable to T2b SCCs in the first phase of the trial assessing the effectiveness of surgery with a 10mm surgical margin as compared to MMS since the likely failure rate for MMS is the same as for ART. Given that the case series (chapter 7) indicated that there was a significant trend towards higher risks of local and regional recurrence after surgical excision from T2a to T2b, T2 SCCs will be stratified into T2a and T2b in the first stage of the trial to test the null hypothesis that there is no significant difference in outcomes after wide surgical excision or MMS for T2a and T2b SCCs separately. For T2a tumours, a two sample continuity corrected chi-squared test with a 5% significance level based on an odds ratio of 1.42 for local recurrence (15% MMS versus 20% surgery) will have 80% power when the sample size is 1890 (945 per group) or 90% power when a sample size of 2504 (1252 per group) is used ().

To determine how many participants are needed for the entire trial, the sample sizes above for T2b SCCs need to be multiplied by a factor of 1.14% to allow for 86% complete clearance rates. Thus the total T2b sample sizes needed are 2595 (1296 per group) for 80% power and 3354 (1677 per group) for 90% power. Assuming that approximately 48% of all T2 SCCs are T2b (chapter 7), these figures therefore need to be multiplied by a factor of 2.08 for an estimate of the total number of T2 SCCs that would be required to yield an adequate number of T2b tumours (which would automatically also give an adequate number of T2a tumours). Therefore a total of 5400 T2 SCCs would be required for 80% power for each stage of the trial, and 6988 for 90%

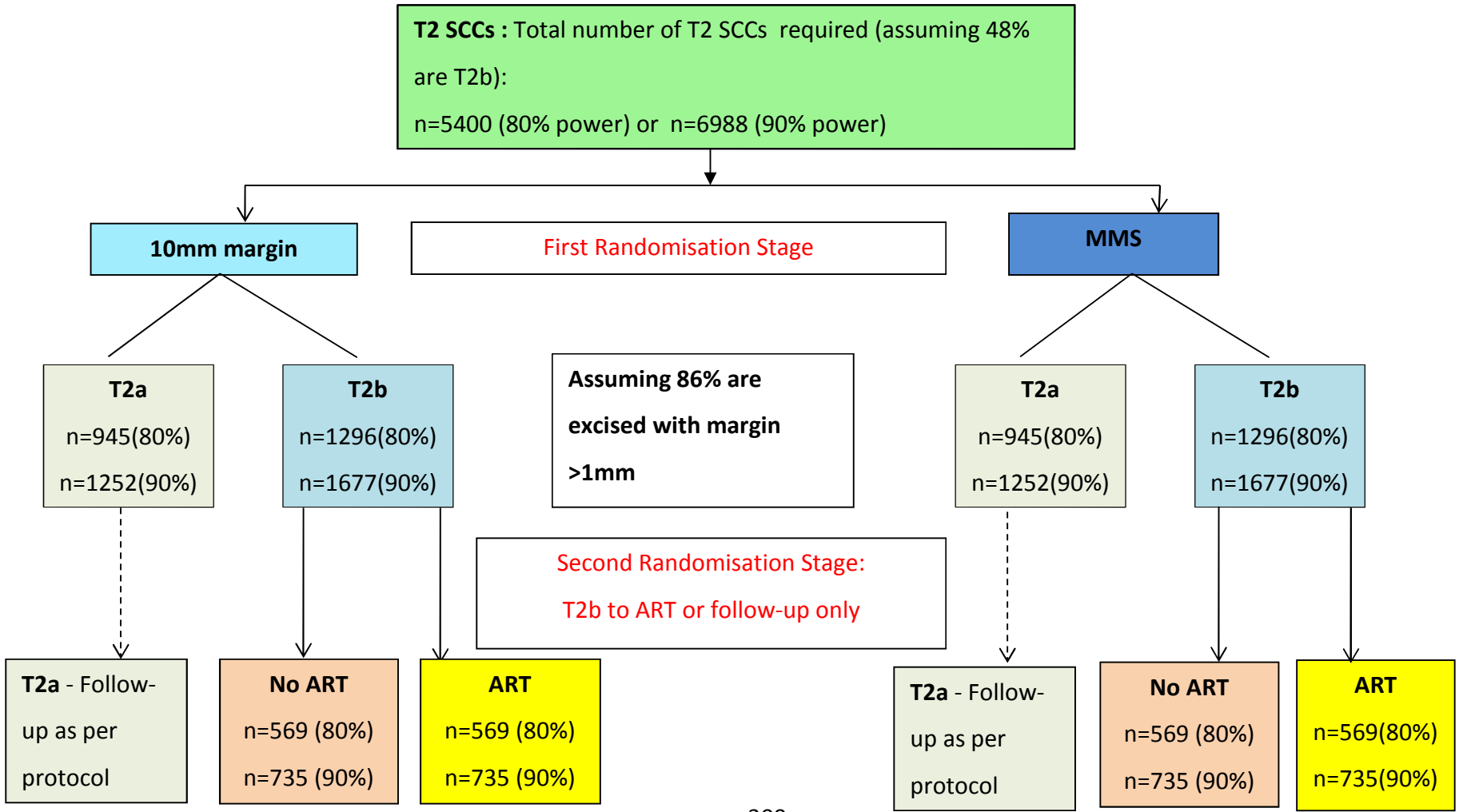
power. The estimated number of patients at each stage is outlined in Figure 55. The final number of patients needed to be recruited into the RCT needs to take into account the drop-out rate (for example due to death or withdrawal), since it would not be valid to assume a worst case scenario where all drop-outs are assumed to have had a recurrence. If a drop-out rate of 10% is assumed then the above estimates would need to be further multiplied by a factor of 1.1%, or 1.25% if a drop-out rate of 20% is assumed.

Feasibility work with patients (chapter 8) indicated that approximately 55% were hypothetically willing to be randomised into both stages of the trial. However, if it is assumed that this is likely to be an underestimate and that more like one third of patients approached will be in practice be willing to be randomised, then it will be necessary to approach approximately 18000 patients in total to accrue the sample size required for the study to have 80% power. Thus, it will be necessary to approach approximately 3600 patients per annum over a recruitment 5-year period. Data from the case series analysis in Nottingham indicated that there are approximately 270 patients per annum who would theoretically be eligible for the trial. Therefore, it is estimated that recruitment would need to take place from 13 centres to accrue the required number of participants.

Trial participants will be analysed in the groups to which they were randomised regardless of which treatment they received and all will be included in the analysis on an intention-to-treat basis.

All analyses will be documented in the Statistical Analysis Plan which will be finalised prior to database lock. This will also include methods to deal with missing data and sensitivity and sub-group analyses where appropriate.

Figure 55: Estimated sample sizes at each stage of the trial



9.2.11. Ethical Arrangements

The main ethical issues are:

- That eligible patients should be aware of the uncertainty regarding the best approach to the management of high-risk primary SCCs
- That trial participation must not delay the pathway to the definitive treatment of SCC

The key members of the SSMDT managing SCC, typically dermatologists, clinical oncologists and plastic surgeons, will be local investigators. Approval by the Research Ethics Committee (REC) and local Research and Development (R&D) team will be obtained before investigators enrol participants. Clinicians will retain responsibility to take immediate action to protect the health and interest of individual participants.

9.2.12. Risk and anticipated benefits for participants

Surgery is the current mainstay of treatment for patients with SCC of the skin and is generally safe. However, there is a small risk of excessive bleeding and infection. Some tumours, particularly those that are large or in cosmetically complex areas may require a flap or graft for repair. Furthermore, patients who are unable to lie down due to a comorbid condition may not tolerate Mohs micrographic surgery which is a potentially lengthy procedure.

Radiotherapy is an established treatment modality for cutaneous SCC, either on its own or as adjuvant therapy, and is generally well tolerated in this context. As multiple treatment sessions are required patient convenience may be compromised. Ionising radiation is also associated with a small increased risk of cutaneous carcinoma within the treatment field. Atrophy, hypopigmentation, alopecia, and telangiectases are also commonly seen late cutaneous sequelae of radiotherapy, which may be unacceptable for younger patients. Due to the risk of radionecrosis, radiotherapy is not advisable for lesions overlying bone or cartilage.

Participants will be made aware of the risks in the participant information resources and when they are counselled for informed consent and incidence of adverse events will be monitored throughout the trial.

Potential benefits to participants cannot be guaranteed, although all participants will have surgical excision to manage their primary disease. Participants who experience emotional distress as a result of participating in the trial will be offered details of a counselling service.

9.2.13. Informed Consent

The nature and purpose of both stages of the trial will be explained to potential participants when they are first approached to take part. However, they will be required to give their written informed consent separately for each stage of the trial if applicable. All participants will give their written informed consent prior to randomisation to one of the two surgical arms. Participants who are then eligible to take part in the second stage of the trial on the basis of their high-risk pathology, will give written informed consent prior to randomisation to receive adjuvant radiotherapy or no adjuvant radiotherapy. A trained member of the research team will counsel participants about the reasons that the trial is being conducted, potential risks associated with the interventions, and the purpose of randomisation. Participants will have time to consider whether they wish to give their informed consent, and will have access to a member of the research team to discuss further if required. Participants' rights to decline trial participation without giving a reason will be respected.

9.2.14. Informing Participants of possible benefits and risks

Participant Information Leaflets (PILs) will be prepared in line with current guidelines and will be informed by the results of the feasibility study which was undertaken as part of this project. These will contain information about the trial, how the trial may affect patients, and outline likely benefits and risks to participants. The trial will also have a dedicated website containing this information and details of the research team.

9.2.15. Research Governance

The trial will be run in accordance with the sponsor's standard operating procedures (SOPs), and managed through a Clinical Trial Unit with expertise in cancer trials. An independent Trial Steering Committee (TSC) will be established prior to initiation of the trial, which will oversee the conduct of the trial. A Data Monitoring Committee will be set up to ensure participant safety throughout the trial.

9.2.16. Confidentiality of Data

All participants' data will be handled and stored in accordance with the sponsor's SOPs and the Data Protection Act. Trial documentation will be retained using secure archiving facilities for 7 years.

9.2.17. Trial Regulation Requirements

As the trial involves radiation, a Medical Physics Expert (a registered clinical scientist registered with the Health Professions Council) will be involved with writing the ethics application and a study contact.

The trial will be registered on an approved trial registry prior to the start of recruitment and the protocol and analysis plan will be published in full.

9.3 Ongoing discussions about the proposed trial

The trial proposal outlined above has been extensively discussed with multidisciplinary colleagues in order to get it to its current stage. However, there are still some ongoing discussions between dermatology surgeons and plastic surgeons regarding exact surgical margin size on the head and neck, and the appropriateness of including Mohs as a comparator for cutaneous SCCs not located on the head or neck.

The reluctance of some clinicians to excise with a wide margin on cosmetically sensitive areas such as the face has been alluded to in the results of the analysis of SCCs in this thesis (chapter 7), where the mean excision margin around head and neck SCCs appeared smaller than around those located elsewhere on the body. It has also been noted by others that clinicians will

take more generous margins around truncal SCCs than recommended in current guidelines, with many surgeons admitting that they would take smaller margins than recommended on cosmetically and functionally areas of the face to avoid creating functional problems which may require extensive reconstruction (Hemington-Gorse et al., 2006, Staiano et al., 2004). Reluctance of clinicians to adhere to an excision margin of 10mm could therefore compromise the conduct of the proposed trial. Therefore, at the time of writing this thesis, it is envisaged that for SCCs randomised to be excised by conventional excision, the decision regarding excision margin size will be made upon tumour diameter for head and neck SCCs, so that SCCs larger than 2cm in diameter will be excised with a 10mm margin, whereas those that are 2cm or smaller will be excised with a 6mm margin. This will still provide valuable data regarding the adequacy of each excision margin and will be more attractive to clinicians who are concerned about cosmetic and functional implications.

Furthermore, it may not be appropriate to include Mohs micrographic surgery as one of the surgical treatments for SCCs that are not located on the head and neck and where potential cosmetic and functional sequelae are not likely to be as significant. At the time of writing, consideration is therefore being given to running a second trial of non-head and neck SCCs, in which there will be a direct comparison of 6mm versus 10mm excision margins, as was proposed at an earlier stage of the trial development. This would potentially allow centres to participate which do not have ready access to Mohs facilities, whilst focussing the Mohs resources that are available on the high-risk head and neck SCCs. When agreement has been reached on these points, an application for funding will be submitted during 2014.

CHAPTER 10:

IMPACT OF THE RESEARCH AND CONCLUSIONS

10 IMPACT OF THE RESEARCH AND CONCLUSIONS

10.1 Introduction

Historically, there has been little high-quality research that has addressed the management of SCC as a discrete entity; the assumption that SCC can be likened to BCC and that they can be studied together is fallacious and both warrant researching separately. Faced with a lack of good evidence and management uncertainties, there has much been variation among clinicians regarding SCC management and a more consistent approach to management is called for which is based on a stronger evidence-base than has been the case to date.

Previous chapters in this thesis have outlined the issues that are associated with research into the treatment of cutaneous SCC (chapter 2), and described the research that has been done that will inform an RCT directly comparing surgical treatments and which will also provide evidence on the usefulness or otherwise of post-operative adjuvant radiotherapy for patients with particularly high-risk SCCs.

This final chapter is an overview of the impact that this research has had, and is having, in the field of SCC management, and will also describe how patients have been involved in the research throughout its different stages. Suggestions will also be made on possible directions for future SCC research. Finally I will share a few personal reflections on my involvement with the research and the lessons that I have learned along the way.

10.2 Impact of this research

The work described in this thesis contributes original research to the body of knowledge relating to the management of cutaneous SCC. Furthermore, it is contributing to furthering research into what is such a common tumour throughout the world but which has been so shockingly overlooked in terms of high-quality research. In Figure 56 the research cycle outlined in chapter 2 is revisited, summarising the individual stages of the projects described within this thesis.

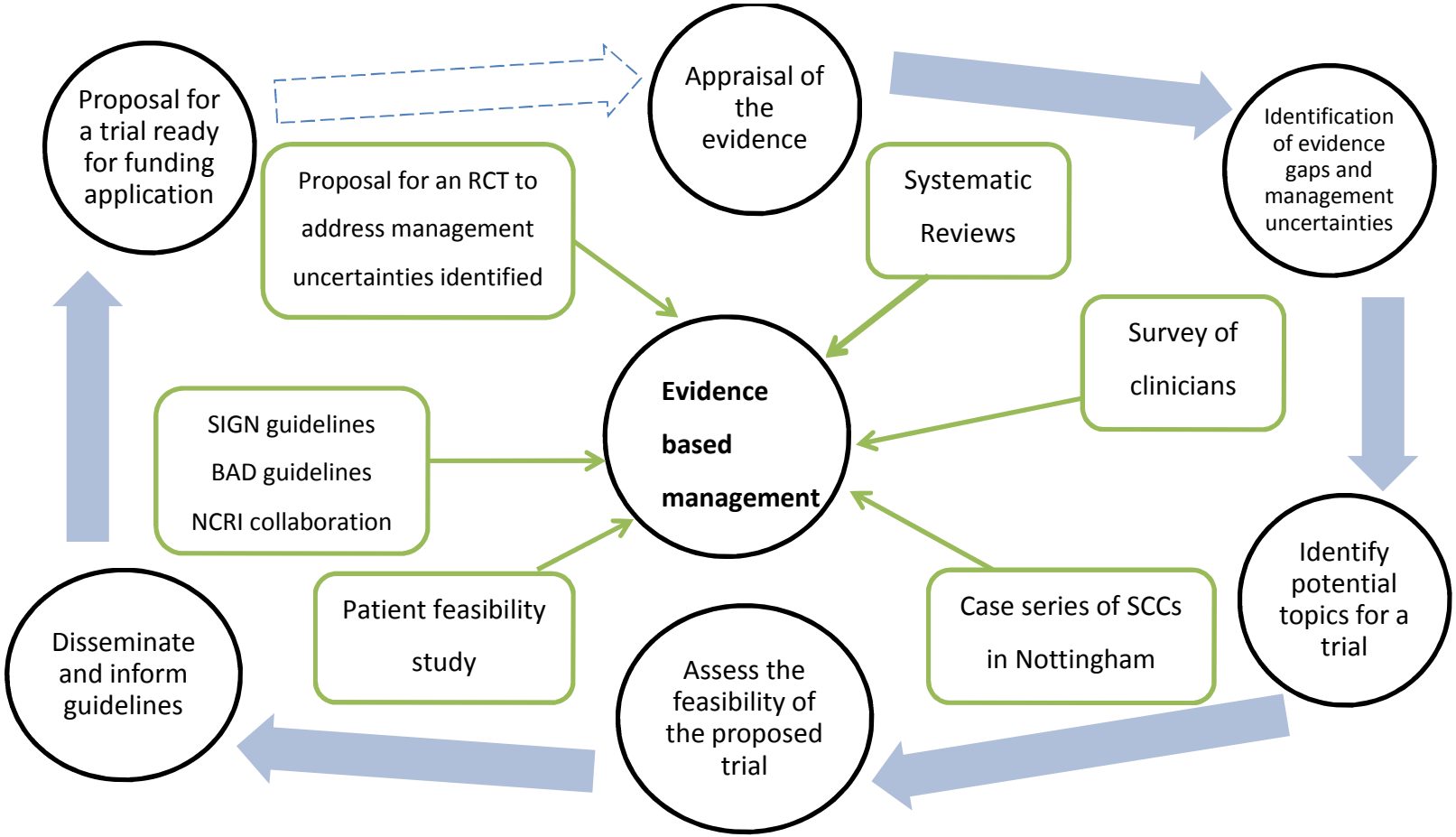


Figure 56 : The research cycle revisited

10.2.1. Guideline development

This body of research commenced with an appraisal of the current evidence-base for primary non-metastatic cutaneous SCC treatments in the form of two systematic reviews; a Cochrane systematic review of RCTs and a large systematic review of case series. These reviews have highlighted the absence of RCTs to compare SCC treatments and have comprehensively evaluated current SCC treatments from the best evidence available, with deductions as far as possible regarding outcomes after different treatments. The Cochrane systematic review was incorporated into the NICE evidence update of their 'Improving Outcomes for People with Skin Cancer including Melanoma' report (National Institute for Health and Clinical Excellence, 2011), to which I contributed as a member of the Evidence Update Advisory Group which appraised and summarised selected new evidence. This emphasised the clear and urgent need for well-designed clinical trials in the area. An impact is now also being seen as new and updated SCC clinical management guidelines are produced. The findings from the evidence appraisal were presented to the Scottish Intercollegiate Guidelines Network Development Group and are referred to extensively in the new SCC guidelines that have recently been published (Scottish Intercollegiate Guidelines Network, June 2014). In addition, the BAD multiprofessional guidelines that are currently being updated and are due to be published in 2015 are utilising the evidence from these systematic reviews. Both sets of management guidelines will have a direct impact on the management of SCC patients.

10.2.2. Implications for Clinical Practice

The current mainstay of treatment for SCC is surgery, either with conventional excision of tumour alone with a margin of normal-looking skin, or Mohs micrographic surgery (MMS). Other treatments in the current management guidelines (Motley et al., 2002) include radiotherapy, either alone or as an adjunct to surgery, curettage and cautery, or cryotherapy. Treatment choice is based upon tumour and patient characteristics. However, treatment practices such as excision margins and adjuvant radiotherapy are

not standardised, and vary according to individual clinicians and, in some cases, the availability of facilities for particular treatments.

The clinician survey and evidence appraisal conducted as part of this research indicated that there are areas of management uncertainty which are not addressed in current guidelines. The proposed RCT will provide much needed evidence to inform future evidence-based guideline development regarding excision margins, the use of MMS and the role of adjuvant radiotherapy in treating high-risk SCCs. Stratification of patients according to their risk will guide clinical practice and will assist with clinical decision-making regarding the most appropriate treatment for individual patients.

10.2.3. Implications for research

This is the largest programme of dedicated clinical research into SCC treatment to date, and has stimulated interest in SCC research.

The identification of gaps in the evidence and areas of treatment uncertainty has resulted in the development of a proposal for the first RCT of its kind for this very common cancer. Important research questions will be addressed in this trial:

- Adequacy of excision margins in surgical excision of high-risk SCCs
- Effectiveness of Mohs surgery compared with surgical excision
- The role of adjuvant radiotherapy.

The results of the case series of SCCs submitted to histopathology have given an indication of the number and types of high-risk SCCs eligible for inclusion in the RCT, and the frequency of outcomes in patients within 5 years after treatment, which is informing development of the protocol.

Patients feel that an RCT of SCC treatment is feasible from the perspective of potential participants. However, they identified that poor understanding of the nature and purpose of randomisation and perceived lack of equipoise regarding the treatment arms could be major barriers to successful recruitment, and will need to be taken into account when presenting the trial

to participants. Furthermore, their information requirements will be taken into account when producing participant resources for the trial, to ensure that these are delivered in the most appropriate formats.

10.3 Patient and public involvement

In contrast to some chronic skin diseases, there is no patient support group for people who are affected by cutaneous SCC. Nevertheless, patients and stakeholders have been involved throughout the research stages described in this thesis whenever possible. In terms of future research, early engagement with all key stakeholders will help to encourage the wide dissemination of the results of the final study, leading to early adoption of the trial findings, and impact on guidelines and policies.

Patients themselves have had, and will continue to have, a vital role throughout the life of the trial. A former skin cancer patient was a co-author on the Cochrane Systematic Review, providing valuable input from a lay person's perspective. Furthermore, the patient representative on the NCRI subgroup has given insightful comments as the trial proposal has developed towards a funding application.

However, patients have had the greatest impact on this research in the design and conduct of the feasibility study. Evaluation of the feasibility of the proposed trial from the perspective of potential participants was considered crucial in guiding the design of the proposed RCT. In addition, the early identification of possible barriers to recruitment was important in order to develop strategies to optimise recruitment, particularly from a target population which is predominantly elderly. The feasibility study took the form of a questionnaire and focus group. We sought the opinion of members of the Centre for Evidence Based Dermatology patient panel, including some who had a history of skin cancer themselves, in an interactive workshop session in which the questionnaire was refined, and delivery of the questionnaire and

focus group was discussed. Patients who had been treated for SCC over the course of the previous 12 months and who were representative of the population from which participants in the proposed RCT will be recruited, took part in the feasibility study. Key points were identified from this work; these have already informed the proposed RCT and will continue to do so as participant resources are developed for the trial:

- Receiving a diagnosis of SCC induces anxiety, and patients may struggle to recall information given at the initial consultation. Repeating information and the use of non-written formats such as videos and audiotapes may help overcome this. The availability of participant information resources in a variety of formats is desirable.
- Information resources must be in plain language that is easily understood by patients from a range of educational backgrounds.
- The concept of randomisation is poorly understood and will need thorough explanation if recruitment to the trial is to be optimised. This may require additional staff and time resources to ensure participants understand and are comfortable with its principles.
- Randomisation to one of the surgical arms of the trials would generally not be problematic for feasibility studies participants, unless the SCC was located in a cosmetically or functionally sensitive area. Fewer participants would feel comfortable about being randomised in the second stage of the trial where they would either receive adjuvant radiotherapy or follow-up alone without adjuvant radiotherapy, mainly due to their perceived fear of receiving radiation. This could impact on the successful recruitment into the latter stage of the proposed RCT, and is being taken into account when writing participants' information sheets: the degree of risk of radiation when used in this context must be carefully explained and the notion of clinical equipoise reinforced.
- In view of the advanced age of potential participants in the proposed RCT, exclusion criteria in terms of existing co-morbidities should not

be too rigid, and extra staff and time input may be required to allay the concerns of older patients.

- Financial arrangements should be in place to cover the costs of extra hospital visits that may be incurred by participants randomised to receive adjuvant radiotherapy.
- Importantly, potential participants did not reject the proposed RCT as being unfeasible from a patient's perspective.

This research has shown that patients with SCC would like to know more about their condition, but also that there is interest in helping with future research. It will be important to include a patient representative on the Trial Steering Committee. Furthermore, from the work there is now a group of patients from the focus group who are willing to review documents and other resources produced for participants in the trial.

10.4 The future of SCC research

Given the current lack of studies of good methodological quality, there is certainly scope for the development of further SCC research in the future. Some possible areas for future research that have emerged as a consequence of this research are suggested below:

- How is the incidence of cutaneous SCC changing in the UK, and is the demography of patients who are affected changing? From the analysis of SCCs treated in Nottingham during two 12-month periods (chapter 7), there is a suggestion that numbers overall are increasing, and that the mean age of affected patients may be rising.
- The clinician survey (chapter 5) has indicated that, apart from the areas of uncertainty that will investigated in the proposed trial being developed as part of this research, there is also interest in the role of newer agents such as cetuximab to treat SCC.
- The clinician survey (chapter 5) also highlighted a desire for the optimisation of follow-up schedules for SCCs according to their risk of

recurrence. As clinicians' workloads increase, there is a need for more evidence to support the frequency of follow-up and total duration of follow-up.

- Furthermore, the qualitative work with patients (chapter 8) suggested that patients have poor knowledge of their condition even when they have experienced treatment of several skin cancers. Patients themselves need to be aware of the potential for recurrence and second primary tumours between clinician follow-up appointments or after follow-up. Educational tools aimed at patients or their carers may be valuable if they improve their ability and confidence to recognise abnormalities at an early stage, but would warrant evaluation of their mode of delivery, effectiveness and acceptability with patients.

Patient-reported outcomes and QoL measures were lacking in the studies that were appraised in the systematic reviews conducted as part of this thesis (chapters 3 and 4). They should, however, be integral to future SCC research as they are recognised as having the potential to improve the quality of the research by providing evidence from the patient's perspective. Additionally, with an ageing population and as the burden of SCC on health service provision continues to grow, evaluation of cost-effectiveness of different treatments will be an important consideration.

10.5 Personal reflections

Throughout the course of this research I have been very privileged to have had the opportunity to acquire and develop a new set of skills and competencies that have enriched me both as a researcher and as an individual. The nature of the research has called for a broad range of methodologies; from systematic reviewing through the qualitative and quantitative methods to the trial development, every stage has had its challenges to overcome. One of the main lessons I have learned is that it is sometimes necessary to take a more flexible approach and to keep an open

mind regarding alternative ways of meeting challenges, but that with perseverance and patience these challenges will be surmounted.

I have certainly become more adept at dealing with large amounts of information and data, and my information management skills were definitely honed whilst dealing with the huge number of potential studies encountered whilst conducting the systematic review of observational studies. The development of a more systematic mind-set than I previously possessed was a great by-product of this work.

The feasibility work with patients afforded me the opportunity to experience writing a study protocol and regulatory approvals and to manage a study, teaching me that it is imperative to liaise with others involved in the process at an early stage in order to facilitate as smooth a passage as possible through the bureaucratic necessities.

Collaboration and networking with colleagues from many disciplines has been an important part of this research, and although I have been responsible for developing and conducting each of the individual stages, the overall objectives of the work could not have been achieved without the involvement and co-operation of others. This was particularly true for the clinician survey, where I needed to liaise with those influential in their respective professional organisations, and during the development of the trial proposal, in which it was imperative to bring together those who will ultimately be responsible for recruiting into and delivering the definitive trial. In an area where there are so many evidence gaps, this has generated much debate and I have learned that it takes much patience and negotiation to achieve some sort of consensus among those who may hold strong professional opinions, and that the time required to reach this stage should never be underestimated.

Through my work, I have been fortunate to have had the opportunity to meet and to learn from those who are eminent in the field of NMSC, both within the university and on a wider scale and to develop my own reputation in the area. In 2010 I was invited to sit on the NICE skin cancer evidence update

group which was charged with updating the 2006 NICE guidance 'Improving Outcomes for People with Skin Cancer', through which I learned the steps that are involved in generating NICE guidance. Additionally I was invited to present the findings from my systematic review of observational studies to the SIGN development group in Scotland, which has subsequently incorporated the results of the work into their management guidelines that have just been published. I have also been invited to participate in the development of the BAD management guidelines that are currently in the process of being updated.

By presenting my research at various meeting and conferences I have had the opportunity to disseminate the findings to a wider audience and to refine my presentation skills. I believe that presentation to international audiences requires a slightly different presentation approach in order to convey the message of the research to those who do not necessarily speak English as their native language. It has therefore been a great privilege to present my research at international conferences, and I have been very fortunate to have been awarded a Graduate School Travel prize and a Nottingham Centre of Evidence-Based Health Care Scholarship that have enabled me to do this.

Ultimately the patient is at the heart of the practice of evidence- based medicine. Listening to patients, communicating with them and getting them involved in the research really brought this into focus for me when I conducted the feasibility study and was one of the most rewarding parts of the work. If my research can in some way contribute to improving the management and quality of life of these patients, then the (mostly) highs and (occasional) lows of the past few years will truly have been worthwhile.

10.6 Concluding remark

Patients affected by cutaneous SCC clearly deserve to receive treatments that are both appropriate for them, and supported by good quality evidence. However, cutaneous SCC does not behave in the same way as other skin cancers such as BCC, and the evidence base for treatments is currently very poor. The work in this research is helping to redress this situation, by informing guidelines and future clinical decision-making and by generating a step-change in data needed to effectively plan for a definitive national RCT.

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APPENDICES

APPENDIX 1

INTERVENTIONS FOR NON-METASTATIC SQUAMOUS CELL CARCINOMA OF THE SKIN (COCHRANE SYSTEMATIC REVIEW) SEARCH STRATEGIES

Specialised Skin Register search strategy

(squamous and cell and carcinoma) or (skin and neoplasm*) or (skin and cancer*) or (skin and tumour*) or (skin and tumor*) or (non-metastatic and squamous and cell and carcinoma) or (NMSC) or (non-melanoma and skin and cancer) AND (cryotherapy or (moh* and surg*) or (excis* and surg*) or curettage or cauter* or electrosurgery or electrodesiccation or photodynamic or photochemotherapy or (laser* and surg*) or (laser* and therap*) or radiotherapy or (intralesional and chemotherap*) or interferon* or retinoi* or fluorouracil or bleomycin or (solasodine and glycoside*) or (drug* and therap*))

Cochrane Library search strategy

#1(squamous cell carcinoma) or (skin cancer$) or (skin neoplasm$) or (skin (tumour$ or tumor$))
#2(non-metastatic squamous cell carcinoma) or (NMSC) or (non-melanoma skin cancer)
#3MeSH descriptor Carcinoma, Squamous Cell explode all trees
#4MeSH descriptor Skin Neoplasms explode all trees
#5(#1 OR #2 OR #3 OR #4)
#6(cryotherapy) or (cryosurgery) or (moh$ and surgery) or (excision$ and surgery)
#7(curettage) or (cauter$)
#8(electrosurgery) or (electrodesiccation) or (photodynamic therapy) or (photochemotherapy)
#9(laser surgery) or (laser therapy) or (radiotherapy) or (interferon$)
#10(intralesional chemotherapy) or bleomycin or fluorouracil or (solasodine glycoside$) or retinoi$ or cisplatin
#11MeSH descriptor Cryotherapy explode all trees
#12MeSH descriptor Cryosurgery explode all trees
#13MeSH descriptor Mohs Surgery explode all trees
#14MeSH descriptor Curettage explode all trees
#15MeSH descriptor Cautery explode all trees

#16MeSH descriptor Electrosurgery explode all trees
#17MeSH descriptor Photochemotherapy explode all trees
#18MeSH descriptor Laser Therapy explode all trees
#19MeSH descriptor Radiotherapy explode all trees
#20MeSH descriptor Interferons explode all trees
#21(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #25)
#22(#5 AND #21)
#23SR-SKIN
#24(#22 AND NOT #23)
#25MeSH descriptor Drug Therapy, this term only

MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. squamous cell carcinoma.mp. or exp Carcinoma, Squamous Cell/
12. skin neoplasms.mp. or exp Skin Neoplasms/
13. skin cancer$.mp.
14. (skin tumour$ or skin tumor$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. non-metastatic squamous cell carcinoma.mp.
16. NMSC.mp.
17. non-melanoma skin cancer.mp.
18. cryotherapy.mp. or exp Cryotherapy/
19. cryosurgery.mp. or exp Cryosurgery/
20. moh's surgery.mp. or exp Mohs Surgery/
21. exp Mohs Surgery/ or mohs.mp.
22. excision$ surgery.mp.
23. curettage.mp. or exp Curettage/
24. cautery.mp. or exp Cautery/
25. cauter$.mp.
26. exp Electrosurgery/ or electrodesiccation.mp.
27. photodynamic therapy.mp. or exp Photochemotherapy/
28. laser surgery.mp. or exp Laser Therapy/
29. radiotherapy.mp. or exp Radiotherapy/
30. intralesional chemotherapy.mp.
31. interferon.mp. or exp Interferons/
32. drug therapy.mp. or exp Drug Therapy/

33. 11 or 16 or 13 or 17 or 12 or 15 or 14
34. 27 or 25 or 32 or 28 or 21 or 26 or 20 or 22 or 18 or 30 or 24 or 19 or 23 or 31 or 29
35. 33 and 34 and 10
36. limit 35 to yr="2005 -Current"

EMBASE search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. squamous cell carcinoma.mp. or exp Carcinoma, Squamous Cell/
15. skin neoplasms.mp. or exp Skin Neoplasms/
16. skin cancer$.mp.
17. (skin tumour$ or skin tumor$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
18. non-metastatic squamous cell carcinoma.mp.
19. NMSC.mp.
20. non-melanoma skin cancer.mp.
21. cryotherapy.mp. or exp Cryotherapy/
22. cryosurgery.mp. or exp Cryosurgery/
23. moh's surgery.mp. or exp Mohs Surgery/
24. exp Mohs Surgery/ or mohs.mp.
25. excision$ surgery.mp.
26. curettage.mp. or exp Curettage/
27. cautery.mp. or exp Cautery/
28. cauter$.mp.
29. exp Electrosurgery/ or electrodesiccation.mp.
30. photodynamic therapy.mp. or exp Photochemotherapy/
31. laser surgery.mp. or exp Laser Therapy/
32. radiotherapy.mp. or exp Radiotherapy/
33. intralesional chemotherapy.mp.

34. interferon.mp. or exp Interferons/
35. drug therapy.mp. or exp Drug Therapy/
36. 14 or 19 or 16 or 20 or 15 or 18 or 17
37. 30 or 28 or 35 or 31 or 24 or 29 or 23 or 25 or 21 or 33 or 27 or 22 or 26 or 34 or 32
38. 36 and 37 and 13
39. limit 38 to yr="2007 -Current"

PsychInfo and AMED search strategy

1. random$.mp. 2. factorial$.mp. 3. placebo$.mp. or PLACEBO/ 4. (doubl$ adj blind$).mp. 5. (singl$ adj blind$).mp. 6. (assign$ or alloc$).mp. 7. volunteer$.mp. or VOLUNTEER/ 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. squamous cell carcinoma.mp. or exp Carcinoma, Squamous Cell/ 10. skin neoplasms.mp. or exp Skin Neoplasms/ 11. skin cancer$.mp. 12. (skin tumour$ or skin tumor$).mp. 13. 9 or 10 or 11 or 12 14. 8 and 13

LILACS search strategy

Skin Neoplasms/ [Subject descriptor] Carcinoma, Squamous Cell [Subject Descriptor]

Ongoing Trials Register searches

The metaRegister of Controlled Trials on www.controlled-trials.com (April 2009) using the search terms:SCC, Squamous cell carcinoma, skin cancer, skin neoplasms, NMSC

The Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskintrials in the category 'squamous cell carcinoma'

The Australian and New Zealand Clinical Trials Registry on www.anzctr.org.au using the search terms: "squamous cell carcinoma of the skin", "cutaneous SCC", "non-melanoma skin cancer", "NMSC"

The World Health Organisation International Clinical Trials Registry platform on www.who.int/trialsearch using the search terms: squamous cell carcinoma,cutaneous squamous cell carcinoma, SCC, non-melanoma skin cancer, NMSC

The U.S.National Institutes of Health ongoing trials register on www.clinicaltrials.gov using the search terms: 'squamous cell carcinoma AND skin', 'cutaneous' AND squamous cell carcinoma', 'non-melanomatous skin cancer', 'skin neoplasms'

APPENDIX 2

INTERVENTIONS FOR NON-METASTATIC SQUAMOUS CELL CARCINOMA OF THE SKIN: A SYSTEMATIC REVIEW AND POOLED ANALYSIS OF OBSERVATIONAL STUDIES SEARCH STRATEGIES

MEDLINE

1. exp epidemiologic studies/

2. exp case-control studies/

3. exp cohort studies/

4. case control.tw.

5. (cohort adj (study or studies)).tw.

6. Cohort anal$.tw.

7. (Follow up adj (study or studies)).tw.

8. (observational adj (study or studies)).tw.

9. Longitudinal.tw.

10. Retrospective.tw.

11. Cross sectional.tw.

12. Cross-sectional studies/

13. or/1-12

14. (squamous cell carcinoma or skin cancer$ or skin neoplasm$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

15. (skin tumour$ or skin tumor$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

16. (non-metastatic squamous cell carcinoma or NMSC or non-melanoma skin cancer).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

17. exp Carcinoma,Squamous Cell/

18. exp Skin neoplasms/

19. 14 or 15 or 16 or 17 or 18

20. (cryotherapy or cryosurgery or (moh$ and surgery) or (excision$ and surgery)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

21. (curettage or cauter$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

22. (electrosurgery or electrodesiccation).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

23. (photodynamic therapy or photochemotherapy).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

24. (laser surgery or laser therapy or radiotherapy or interferon$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

25. (intralesional chemotherapy or bleomycin or fluorouracil or solasodine glycoside$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

26. (retinoi$ or cisplatin).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

27. exp Cryotherapy/

28. exp Cryosurgery/

29. exp Mohs Surgery/

30. excision$ surgery.mp.

31. exp Curettage/

32. exp Cautery/

33. exp Electrosurgery/

34. exp Photochemotherapy/

35. exp Laser Therapy/

36. exp Radiotherapy/

37. Interferons/

38. exp Interferons/

39. Drug Therapy/

40. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. 13 and 19 and 40

42. Epidural Neoplasms/ or Salivary Gland Neoplasms/ or Nasopharyngeal Neoplasms/ or Perivascular Epithelioid Cell Neoplasms/ or Nervous System Neoplasms/ or Cerebral Ventricle Neoplasms/ or Retinal Neoplasms/ or Central Nervous System Neoplasms/ or Gingival Neoplasms/ or Jejunal Neoplasms/ or Neoplasms, Fibrous Tissue/ or Digestive System Neoplasms/ or Laryngeal Neoplasms/ or Choroid Plexus Neoplasms/ or Palatal Neoplasms/ or Neoplasms, Mesothelial/ or Urethral Neoplasms/ or Tracheal Neoplasms/ or Endometrial Neoplasms/ or Brain Stem Neoplasms/ or Neoplasms, Neuroepithelial/ or Oropharyngeal Neoplasms/ or Uveal Neoplasms/ or Maxillary Neoplasms/ or Sublingual Gland Neoplasms/ or Pelvic Neoplasms/ or Cecal Neoplasms/ or Urogenital Neoplasms/ or "Neoplasms, Ductal, Lobular, and Medullary"/ or Stomach Neoplasms/ or Liver Neoplasms, Experimental/ or Neoplasms, Adipose Tissue/ or Nerve Sheath Neoplasms/ or

Neoplasms, Bone Tissue/ or Mammary Neoplasms, Animal/ or Mediastinal Neoplasms/ or Submandibular Gland Neoplasms/ or Sigmoid Neoplasms/ or Adrenal Gland Neoplasms/ or Cerebellar Neoplasms/ or Pancreatic Neoplasms/ or Neoplasms, Experimental/ or Tonsillar Neoplasms/ or Spinal Neoplasms/ or Bronchial Neoplasms/ or Parathyroid Neoplasms/ or Mouth Neoplasms/ or Thyroid Neoplasms/ or Hypothalamic Neoplasms/ or Common Bile Duct Neoplasms/ or Supratentorial Neoplasms/ or Respiratory Tract Neoplasms/ or Optic Nerve Neoplasms/ or Skull Base Neoplasms/ or Pleural Neoplasms/ or Neoplasms, Connective Tissue/ or Urologic Neoplasms/ or Abdominal Neoplasms/ or Colorectal Neoplasms, Hereditary Nonpolyposis/ or Neoplasms, Radiation-Induced/ or Retroperitoneal Neoplasms/ or Vascular Neoplasms/ or Vulvar Neoplasms/ or Hematologic Neoplasms/ or Bone Marrow Neoplasms/ or Fallopian Tube Neoplasms/ or Gestational Trophoblastic Neoplasms/ or Peritoneal Neoplasms/ or Appendiceal Neoplasms/ or Esophageal Neoplasms/ or Colonic Neoplasms/ or Mammary Neoplasms, Experimental/ or Biliary Tract Neoplasms/ or Cranial Nerve Neoplasms/ or "Neoplasms, Cystic, Mucinous, and Serous"/ or Pharyngeal Neoplasms/ or Neoplasms, Unknown Primary/ or Lung Neoplasms/ or Ovarian Neoplasms/ or Penile Neoplasms/ or Neoplasms, Nerve Tissue/ or Brain Neoplasms/ or Parotid Neoplasms/ or Urinary Bladder Neoplasms/ or Testicular Neoplasms/ or Neoplasms, Muscle Tissue/ or Hypopharyngeal Neoplasms/ or Otorhinolaryngologic Neoplasms/ or Neoplasms, Gonadal Tissue/ or "Neoplasms, Complex and Mixed"/ or Soft Tissue Neoplasms/ or Trophoblastic Neoplasms/ or Rectal Neoplasms/ or Ileal Neoplasms/ or Gallbladder Neoplasms/ or Mandibular Neoplasms/ or Neoplasms, Second Primary/ or Breast Neoplasms/ or Genital Neoplasms, Female/ or Intestinal Neoplasms/ or Kidney Neoplasms/ or "Head and Neck Neoplasms"/ or Maxillary Sinus Neoplasms/ or Choroid Neoplasms/ or Muscle Neoplasms/ or Meningeal Neoplasms/ or Adrenal Cortex Neoplasms/ or Splenic Neoplasms/ or Neoplasms, Hormone-Dependent/ or Peripheral Nervous System Neoplasms/ or Thymus Neoplasms/ or Sweat Gland Neoplasms/ or Endocrine Gland Neoplasms/ or Neoplasms, Vascular Tissue/ or Conjunctival

Neoplasms/ or Sebaceous Gland Neoplasms/ or Duodenal Neoplasms/ or Pituitary Neoplasms/ or Spinal Cord Neoplasms/ or Neoplasms, Fibroepithelial/ or Uterine Neoplasms/ or Gastrointestinal Neoplasms/ or Neoplasms, Basal Cell/ or Liver Neoplasms/ or Ureteral Neoplasms/ or Uterine Cervical Neoplasms/ or Iris Neoplasms/ or Prostatic Neoplasms/ or Thoracic Neoplasms/ or Colorectal Neoplasms/ or Genital Neoplasms, Male/ or Vaginal Neoplasms/ or Heart Neoplasms/ or Breast Neoplasms, Male/ or Orbital Neoplasms/ or Bile Duct Neoplasms/ or "Neoplasms, Germ Cell and Embryonal"/ or Anal Gland Neoplasms/ or Neoplasms, Plasma Cell/ or Paranasal Sinus Neoplasms/ or Bone Neoplasms/ or Infratentorial Neoplasms/ or Tongue Neoplasms/ or Femoral Neoplasms/ or Anus Neoplasms/ or Eye Neoplasms/ or Skull Neoplasms/

43. 41 not 42

44. limit 43 to humans

EMBASE

1. Clinical study/

2. case control study/

3. Family study/

4. Longitudinal study/

5. Retrospective study/

6. Prospective study/

7. Randomized controlled trials/

8. 6 not 7

9. Cohort analysis/

10. (Cohort adj (study or studies)).mp.

11. (Case control adj (study or studies)).tw.

12. (follow up adj (study or studies)).tw.

13. (observational adj (study or studies)).tw.

14. (epidemiologic$ adj (study or studies)).tw.

15. (cross sectional adj (study or studies)).tw.

16. or/1-5,8-15

17. (squamous cell carcinoma or skin cancer$ or skin neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

18. (skin tumour$ or skin tumor$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

19. (non-metastatic squamous cell carcinoma or NMSC or non-melanoma skin cancer).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

20. exp Carcinoma, Squamous Cell/

21. exp Skin Neoplasms/

22. 17 or 18 or 19 or 20 or 21

23. (cryotherapy or cryosurgery or (moh$ and surgery) or (excision$ and surgery)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

24. (curettage or cauter$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

25. (electrosurgery or electrodesiccation).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

26. (photodynamic therapy or photochemotherapy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

27. (laser surgery or laser therapy or radiotherapy or interferon$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

28. (intralesional chemotherapy or bleomycin or fluorouracil or solasodine glycoside$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

29. (retinoi$ or cisplatin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

30. exp Cryotherapy/

31. exp Cryosurgery/

32. exp Mohs Surgery/

33. excision$ surgery.mp.

34. exp Curettage/

35. exp Cautery/

36. exp Electrosurgery/

37. exp Photochemotherapy/

38. exp Laser Therapy/

39. exp Radiotherapy/

40. Interferons/

41. exp Interferons/

42. Drug Therapy/

43. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42

44. 16 and 22 and 43

45. Epidural Neoplasms/ or Salivary Gland Neoplasms/ or Nasopharyngeal Neoplasms/ or Perivascular Epithelioid Cell Neoplasms/ or Nervous System Neoplasms/ or Cerebral Ventricle Neoplasms/ or Retinal Neoplasms/ or Central Nervous System Neoplasms/ or Gingival Neoplasms/ or Jejunal Neoplasms/ or Neoplasms, Fibrous Tissue/ or Digestive System Neoplasms/ or Laryngeal Neoplasms/ or Choroid Plexus Neoplasms/ or Palatal Neoplasms/ or Neoplasms, Mesothelial/ or Urethral Neoplasms/ or Tracheal Neoplasms/ or Endometrial Neoplasms/ or Brain Stem Neoplasms/ or Neoplasms, Neuroepithelial/ or Oropharyngeal Neoplasms/ or Uveal Neoplasms/ or Maxillary Neoplasms/ or Sublingual Gland Neoplasms/ or Pelvic Neoplasms/ or Cecal Neoplasms/ or Urogenital Neoplasms/ or "Neoplasms, Ductal, Lobular, and Medullary"/ or Stomach Neoplasms/ or Liver Neoplasms, Experimental/ or Neoplasms, Adipose Tissue/ or Nerve Sheath Neoplasms/ or Neoplasms, Bone Tissue/ or Mammary Neoplasms, Animal/ or Mediastinal Neoplasms/ or Submandibular Gland Neoplasms/ or Sigmoid Neoplasms/ or Adrenal Gland Neoplasms/ or Cerebellar Neoplasms/ or Pancreatic Neoplasms/ or Neoplasms, Experimental/ or Tonsillar Neoplasms/ or Spinal Neoplasms/ or Bronchial Neoplasms/ or Parathyroid Neoplasms/ or Mouth Neoplasms/ or Thyroid Neoplasms/ or Hypothalamic Neoplasms/ or Common

Bile Duct Neoplasms/ or Supratentorial Neoplasms/ or Respiratory Tract Neoplasms/ or Optic Nerve Neoplasms/ or Skull Base Neoplasms/ or Pleural Neoplasms/ or Neoplasms, Connective Tissue/ or Urologic Neoplasms/ or Abdominal Neoplasms/ or Colorectal Neoplasms, Hereditary Nonpolyposis/ or Retroperitoneal Neoplasms/ or Vascular Neoplasms/ or Vulvar Neoplasms/ or Hematologic Neoplasms/ or Bone Marrow Neoplasms/ or Fallopian Tube Neoplasms/ or Gestational Trophoblastic Neoplasms/ or Peritoneal Neoplasms/ or Appendiceal Neoplasms/ or Esophageal Neoplasms/ or Colonic Neoplasms/ or Mammary Neoplasms, Experimental/ or Biliary Tract Neoplasms/ or Cranial Nerve Neoplasms/ or "Neoplasms, Cystic, Mucinous, and Serous"/ or Pharyngeal Neoplasms/ or Neoplasms, Unknown Primary/ or Lung Neoplasms/ or Ovarian Neoplasms/ or Penile Neoplasms/ or Neoplasms, Nerve Tissue/ or Brain Neoplasms/ or Parotid Neoplasms/ or Urinary Bladder Neoplasms/ or Testicular Neoplasms/ or Neoplasms, Muscle Tissue/ or Hypopharyngeal Neoplasms/ or Otorhinolaryngologic Neoplasms/ or Neoplasms, Gonadal Tissue/ or "Neoplasms, Complex and Mixed"/ or Soft Tissue Neoplasms/ or Trophoblastic Neoplasms/ or Rectal Neoplasms/ or Ileal Neoplasms/ or Gallbladder Neoplasms/ or Mandibular Neoplasms/ or Neoplasms, Second Primary/ or Breast Neoplasms/ or Genital Neoplasms, Female/ or Intestinal Neoplasms/ or Kidney Neoplasms/ or "Head and Neck Neoplasms"/ or Maxillary Sinus Neoplasms/ or Choroid Neoplasms/ or Muscle Neoplasms/ or Meningeal Neoplasms/ or Adrenal Cortex Neoplasms/ or Splenic Neoplasms/ or Neoplasms, Hormone-Dependent/ or Peripheral Nervous System Neoplasms/ or Thymus Neoplasms/ or Sweat Gland Neoplasms/ or Endocrine Gland Neoplasms/ or Neoplasms, Vascular Tissue/ or Conjunctival Neoplasms/ or Sebaceous Gland Neoplasms/ or Duodenal Neoplasms/ or Pituitary Neoplasms/ or Spinal Cord Neoplasms/ or Neoplasms, Fibroepithelial/ or Uterine Neoplasms/ or Gastrointestinal Neoplasms/ or Neoplasms, Basal Cell/ or Liver Neoplasms/ or Ureteral Neoplasms/ or Uterine Cervical Neoplasms/ or Iris Neoplasms/ or Prostatic Neoplasms/ or Thoracic Neoplasms/ or Colorectal Neoplasms/ or Genital Neoplasms, Male/ or Vaginal Neoplasms/ or Heart Neoplasms/ or Breast

Neoplasms, Male/ or Orbital Neoplasms/ or Bile Duct Neoplasms/ or "Neoplasms, Germ Cell and Embryonal"/ or Anal Gland Neoplasms/ or Neoplasms, Plasma Cell/ or Paranasal Sinus Neoplasms/ or Bone Neoplasms/ or Infratentorial Neoplasms/ or Tongue Neoplasms/ or Femoral Neoplasms/ or Anus Neoplasms/ or Eye Neoplasms/ or Skull Neoplasms/

46. 44 not 45

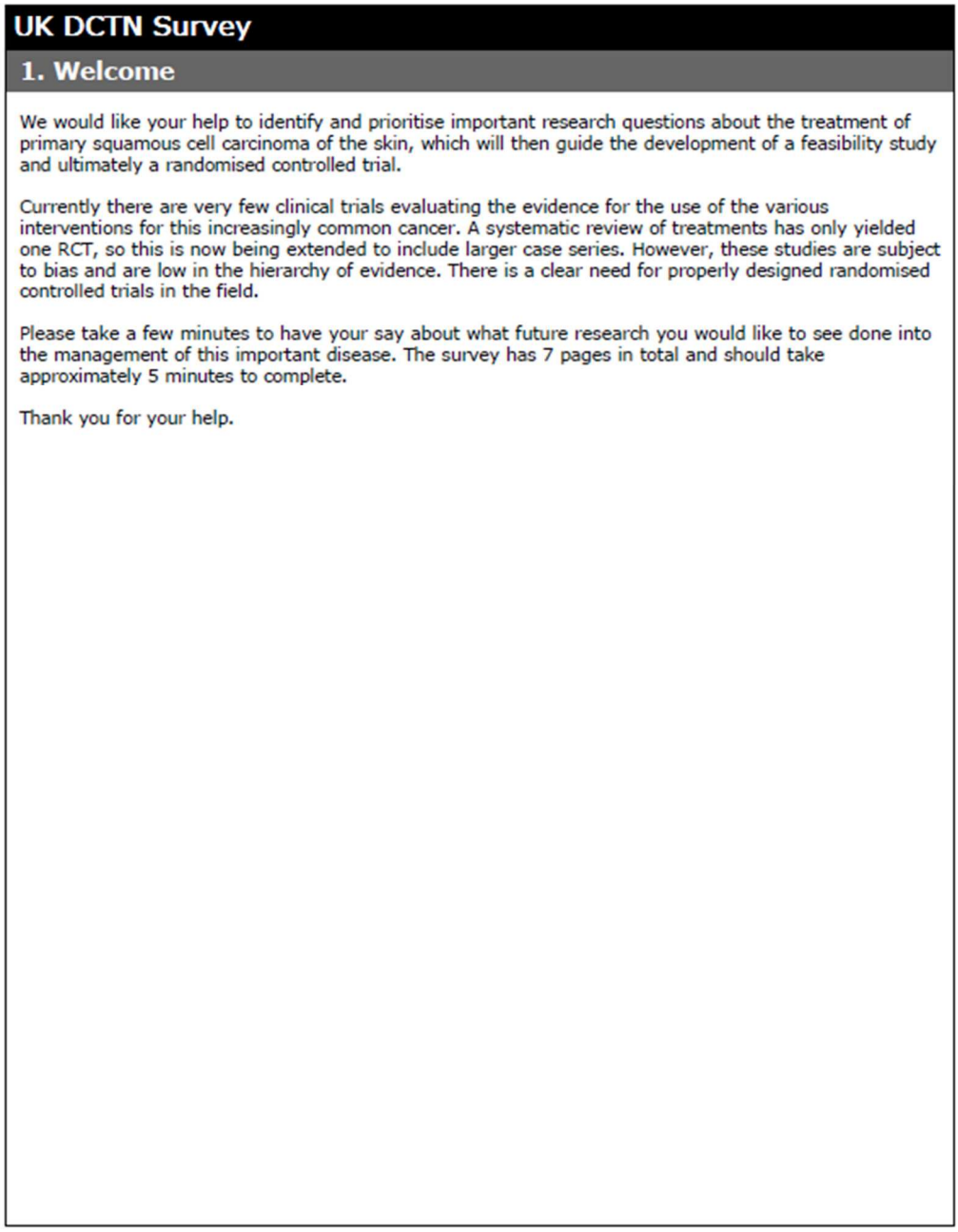
47. exp Lymphoma/

48. 46 not 47

49. limit 48 to humans

APPENDIX 3

SURVEY EXAMPLE



UK DCTN Survey

1. Welcome

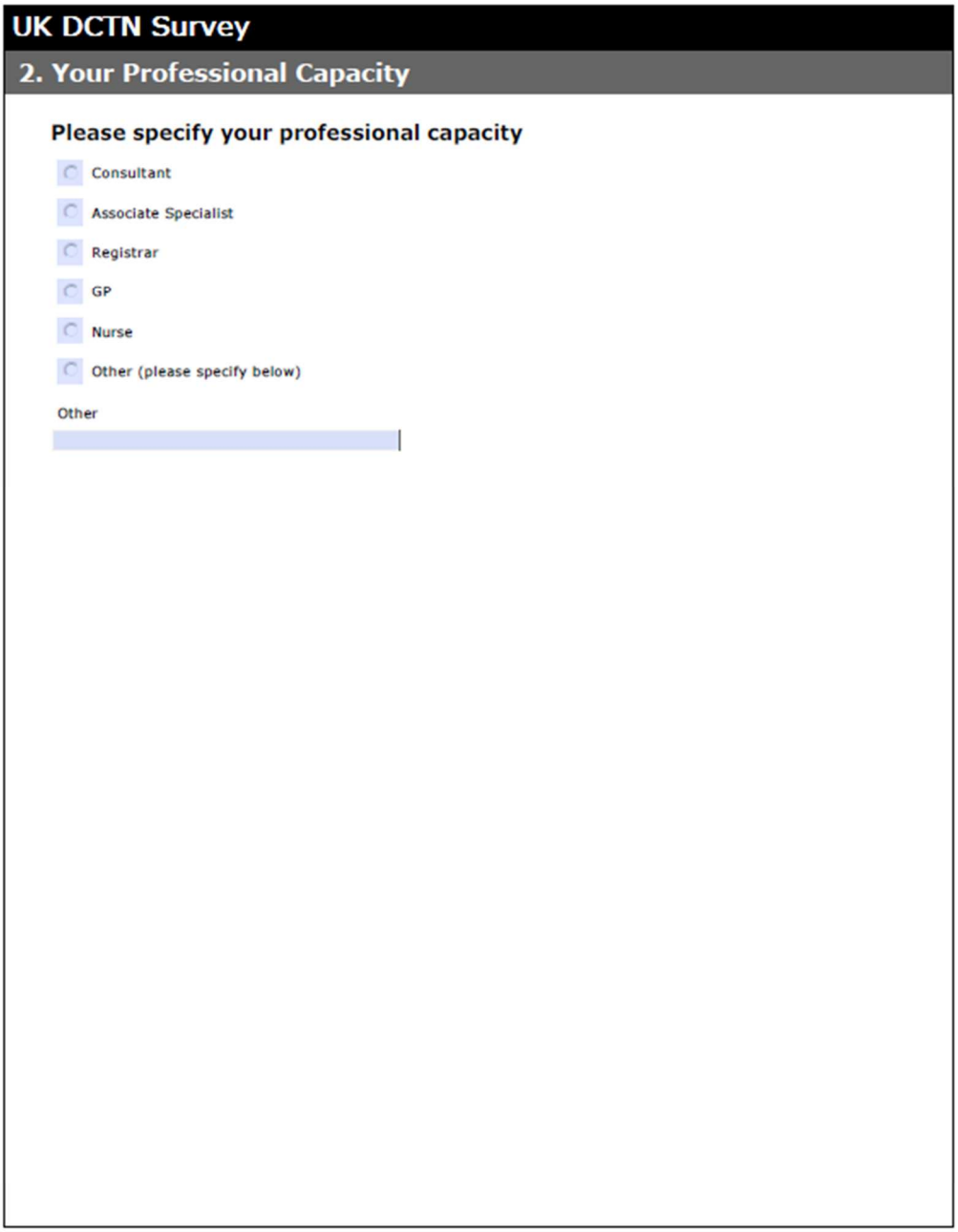
We would like your help to identify and prioritise important research questions about the treatment of primary squamous cell carcinoma of the skin, which will then guide the development of a feasibility study and ultimately a randomised controlled trial.

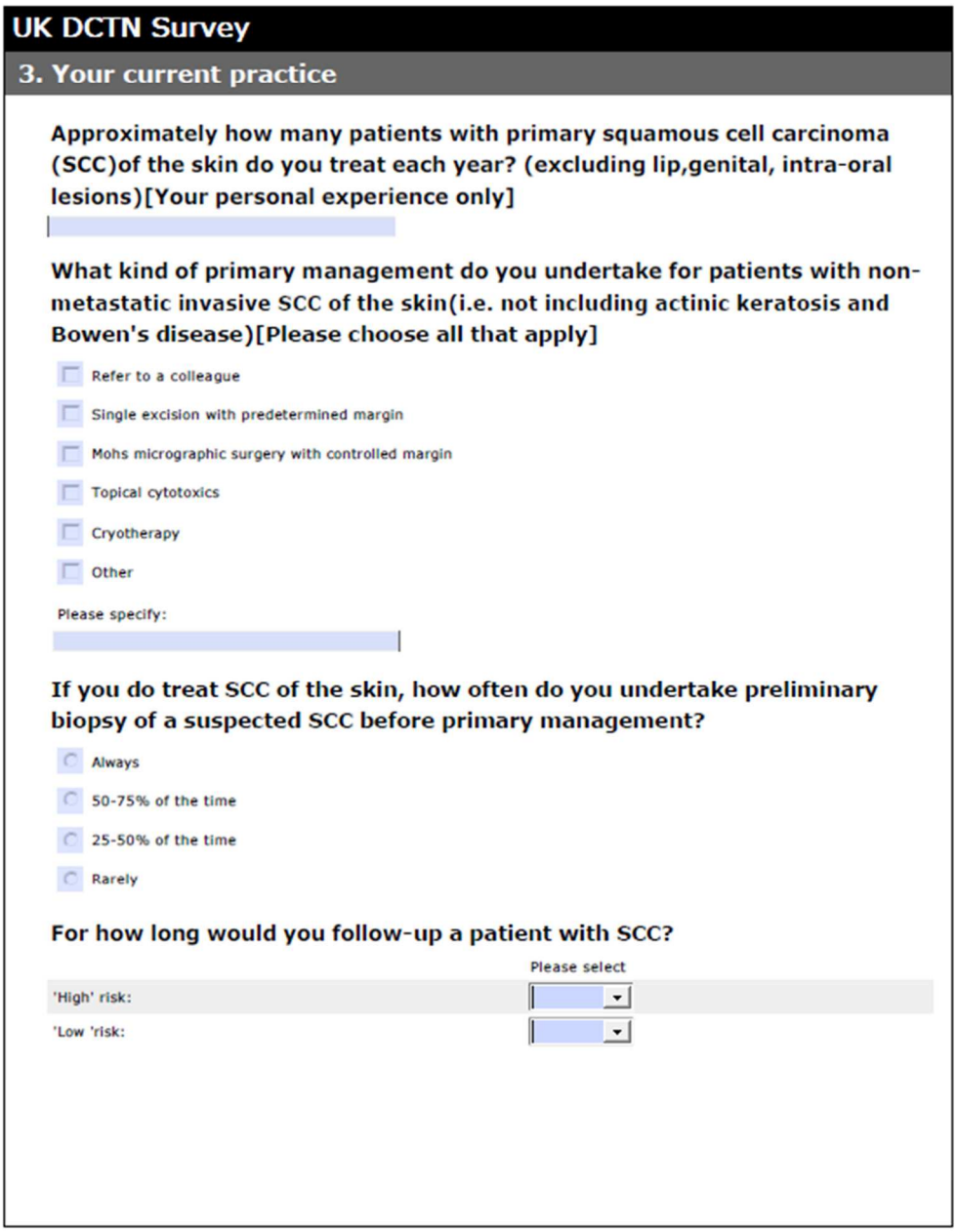
Currently there are very few clinical trials evaluating the evidence for the use of the various interventions for this increasingly common cancer. A systematic review of treatments has only yielded one RCT, so this is now being extended to include larger case series. However, these studies are subject to bias and are low in the hierarchy of evidence. There is a clear need for properly designed randomised controlled trials in the field.

Please take a few minutes to have your say about what future research you would like to see done into the management of this important disease. The survey has 7 pages in total and should take approximately 5 minutes to complete.

Thank you for your help.

Page 1


UK DCTN Survey
2. Your Professional Capacity
Please specify your professional capacity
Consultant
Associate Specialist
Registrar
GP
Nurse
Other (please specify below)
Other
Page 2



UK DCTN Survey

3. Your current practice

Approximately how many patients with primary squamous cell carcinoma (SCC)of the skin do you treat each year? (excluding lip,genital, intra-oral lesions)[Your personal experience only]

What kind of primary management do you undertake for patients with non-metastatic invasive SCC of the skin(i.e. not including actinic keratosis and Bowen's disease)[Please choose all that apply]

- [ ] Refer to a colleague
- [ ] Single excision with predetermined margin
- [ ] Mohs micrographic surgery with controlled margin
- [ ] Topical cytotoxics
- [ ] Cryotherapy
- [ ] Other

Please specify:

If you do treat SCC of the skin, how often do you undertake preliminary biopsy of a suspected SCC before primary management?

- ( ) Always
- ( ) 50-75% of the time
- ( ) 25-50% of the time
- ( ) Rarely

For how long would you follow-up a patient with SCC?

	Please select
'High' risk:	
'Low 'risk:	

Page 3

UK DCTN Survey

4. Your views on research needs

In which of the following areas relating to the treatment of skin SCC do you feel there is the need for a clinical trial? PLEASE GIVE DETAILS OF ANY RESEARCH QUESTIONS YOU MAY HAVE IN THE BOX PROVIDED.

	Yes	No
Optimising surgery	○	○
Role of radiotherapy	○	○
Role of chemotherapy	○	○
Role of newer agents	○	○
Other	○	○

Please give details of your research questions

As a clinician, what would you consider to be the most important outcomes in a clinical trial addressing the treatment of SCC?

	Very important	Important	Fairly important	Not important
Pain of procedure	○	○	○	○
Patient acceptability	○	○	○	○
Survival	○	○	○	○
Local recurrence	○	○	○	○
Regional recurrence	○	○	○	○
Disfigurement	○	○	○	○
Contracture	○	○	○	○
Persistent pain	○	○	○	○
Persistent ulceration	○	○	○	○
Quality of life	○	○	○	○

UK DCTN Survey

5. Your views on research needs (continued)

Are there any other outcomes (e.g. "Burden of Care" issues)that you think should be taken into consideration when designing a trial of interventions for SCC? Please list below:

Would you be interested in recruiting patients to participate in a feasibility study and/or full-scale clinical trial for treatment of SCC?
Please give your contact details if you would like to be involved in a trial in the future.

- ○ Yes, both
- ○ Feasibility study only
- ○ Full-scale RCT only
- ○ Neither
- ○ Maybe

Contact details:

Page 5

UK DCTN Survey

6. Further comments or suggestions

Do you have any further comments or suggestions?

Page 6

UK DCTN Survey

7. Thanks

Your input is very valuable and important to us. Thank you very much for your time in participating in our survey.

APPENDIX 4

NRES approval letter – feasibility study

NHS
Health Research Authority

NRES Committee West Midlands - Coventry & Warwickshire
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839309

31 January 2013

Dr Fiona Bath-Hextall
Associate Professor and Reader in Evidence Based Medicine
University of Nottingham
School of Nursing, Midwifery and Physiotherapy,
The University of Nottingham
Room D83, Queen's Medical Centre,
Nottingham
NG7 2UH

Dear Dr Bath-Hextall

Study title:	**A questionnaire and focus group to explore potential participants' hypothetical willingness to take part in and possible barriers to recruitment for a proposed future randomised controlled trial addressing the management of squamous cell carcinoma of the skin.**
REC reference:	**13/WM/0051**
Protocol number:	**12136**
IRAS project ID:	**107535**

The Proportionate Review Sub-committee of the NRES Committee West Midlands - Coventry & Warwickshire reviewed the above application on 30 January 2013.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Wendy Rees, NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net

Ethical opinion

- The lead reviewer informed the committee this study was a student project.
- The lead reviewer informed the committee this is a feasibility study.
- The lead reviewer informed the committee this is qualitative research.
- The lead reviewer informed the committee the study was well prepared and he was impressed with the writing in A12.
- The committee noted that 20 participants who have had squamous cell carcinoma will be recruited.
- The Committee noted there are 2 proposals either 6mm or 10mm excision

margin of normal looking skin around the carcinoma.

- The Committee agreed this project was well thought through.
- The Committee noted the risks listed and agreed there may be possible distress.
- The Committee agreed the Consent is interesting as if they return the reply slip they wish to take part but that written informed consent will be obtained prior to the focus group.
- The Committee agreed the Participant Information Sheet was appropriate and adequate.
- The Committee noted Participants who take part in the focus group will be paid for travel and parking expenses and will also be offered £25 of high-street vouchers for their inconvenience.
- The Committee agreed this study was very well written.

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site

approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Covering Letter		23 January 2013
REC application	107535/405600/1/640	22 January 2013
Investigator CV	Fiona Bath-Hextall	23 January 2013
Other: CV: Louise Lansbury		23 January 2013
Protocol	1.0	17 January 2013
Letter of invitation to participant	1.0	17 January 2013
Participant Information Sheet	1.0	15 January 2013
Participant Consent Form	1.0	17 January 2013
Interview Schedules/Topic Guides	1.0	17 January 2013
Evidence of insurance or indemnity	Henderson Corporate	25 July 2012
Letter from Sponsor	University of Nottingham	23 January 2013
Questionnaire: Participant Questionnaire	1.0	17 January 2013
Other: Letter accompanying Questionnaire	1.0	17 January 2013
Other: Letter from funder - NIHB		01 August 2008

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.
information is available at National Research Ethics Service website > After Review

13/WM/0051	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp N Rees

Dr Helen Brittain
Chair

Email: NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers" [SL-AR2]

Copy to: *Angela Shone*
Charlotte Davies, Nottingham University Hospitals NHS Trust

APPENDIX 5

Participant Information Sheet

Participant Information Sheet
(Final version 1.0: 17 Jan 2013)

Title of Study: Participant acceptability of a proposed future skin cancer trial

Name of Lead Researcher: Dr Louise Lansbury

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Talk to others about the study if you wish. If anything is not clear after reading this information sheet, one of our team will be happy to go through it with you and answer any questions you may have (contact details are given at the end of this sheet).

What is the purpose of the study?

We are conducting exploratory work to assess whether a future skin cancer trial which we are currently developing would be acceptable to potential participants and what sort of barriers may prevent recruitment into such a trial. This study also forms part of the PhD work of Louise Lansbury, the lead researcher.

Squamous cell carcinoma of the skin (SCC) is a common type of 'non-melanoma skin cancer', the vast majority of which are successfully treated. Usually this involves cutting out the cancer with a margin of normal looking skin (the excision margin). Other types of treatment are sometimes used, and occasionally a group of skin cancer specialists may decide to treat an SCC that has already been surgically excised with some additional radiotherapy.

Occasionally, SCCs that appear to have been treated successfully come back, either in the same area as the original SCC, or they may spread to lymph nodes or a distant organ. This is called 'recurrence' and some SCCs have particular features which makes the chances of this happening more likely. These are called 'higher-risk' SCCs.

Although there are professional UK guidelines which suggest how large the excision margin size should be for SCCs, the evidence upon which these guidelines are based is limited. Similarly, there is uncertainty as to whether some patients are more likely than others to benefit from extra radiotherapy after their surgery. Therefore we are developing a trial to see if we can reduce the risk of recurrence of SCC by comparing recurrence of SCCs that have been cut out with a 6mm margin of normal looking skin with those that have been cut out with a 10mm margin, and then further examining whether patients who have had surgery and who have SCCs with particular high-risk features would benefit by having additional radiotherapy.

We would like patients who have recently been diagnosed with this type of skin cancer to help us make sure that we get the best trial possible by finding out what is important to them about their treatment and whether they would in principle be prepared to take part in such a trial themselves and if not, why not. This will help us to decide if the proposed future trial is feasible to do and whether to pursue our idea further.

The current study involves completing a questionnaire which will be sent by post and returned to the research team. For participants who would like to help us further, we will also run a follow-up focus group to explore issues in greater depth. Please note that if you take part in our current study, you will NOT take part in the trial itself, which is currently only in the early stages of development.

Why have I been invited?

You are being invited to take part because you were recently treated for this particular kind of skin cancer. We will be approaching about 20 people like you who have experienced this condition, asking them to answer some questions about the trial we are proposing and, if they are interested, to take part in a focus group to discuss issues in greater depth.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and your consent to take part will be implied by returning the completed questionnaire. People who complete the questionnaire are under no obligation to take part in the follow-up focus group if they do not wish to, and those who do take part in the focus group will be asked to sign a separate consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

The chart below summarises each stage of your involvement in our study if you agree to take part:

Invitation

The consultant dermatologist who treated you will send you a **letter of invitation** to take part, along with this Participant Information Sheet. ***The research team will only send you the questionnaire after you have given permission for them to have your contact details by returning the enclosed reply slip.***

Postal Questionnaire

Details of the proposed trial and the **questionnaire** itself will be sent by post for you to complete in your own time.

Time to complete questionnaire: 45 minutes to 1 hour

Questionnaire to be **returned** in the pre-paid envelope within 14 days of receipt.

Focus Group

People expressing interest on the questionnaire will be invited to take part in a follow-up focus group with other participants (anticipated 6 or 7) and two researchers. This will take place at Kings' Meadow Campus at the University of Nottingham. Potential participants will be telephoned with further details of the focus group upon receipt of their completed questionnaire, with written confirmation and final details being sent to those able to take part in the week before the meeting. Prior to the discussion written consent will be obtained from each participant. An audio-recording of the discussion will be made to assist with analysis.

Duration: Approx 1-2 hours

If you agree to take part, we would only ask that you are completely honest in response to the questions you are asked. We would rather learn about possible barriers which may prevent people from wanting to take part in the actual study at this early stage rather than when the study is up and running.

You are very welcome to discuss the questionnaire with relatives and friends, but please note that it is only **your** views in which we are interested. Please also note that by taking part in this work you are providing valuable input into the development of a future trial, and that you will not be taking part in the final trial itself.

Expenses and payments

Participants will not be paid to participate in the study. Focus group participants will be reimbursed all out-of-pocket expenses and will also receive £25 in high-street vouchers in recognition of the time given up to attend the group.

What are the possible disadvantages and risks of taking part?

There are no foreseeable risks if you agree to take part. Your clinical care will not be affected in any way if you agree to participate in our research. Please note that the research team will not be able to answer questions about your clinical care. It is important that you keep all other appointments that have been arranged with the doctors involved in your care.

What are the possible benefits of taking part?

Although you will not directly benefit from this study, the information we get from those who take part will help us to understand whether our proposed trial will be acceptable to future skin cancer patients who may be asked to take part, and may raise issues which we will need to take account of when we are designing the trial.

What happens when the research study stops?

Your participation in this study will end when you have completed the questionnaire, or after the focus group if you decide to also take part in this. You will be asked if you would like to receive a summary of the results of this work after all the data has been analysed.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting NHS Complaints. Details can be obtained from the Patient Advice and Liaison Service (PALS) at Nottingham University Hospitals NHS Trust, Freepost, NEA 14614, Nottingham NG7 1BR (tel: 0115 9249924 ext 65412)

Will my taking part in the study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, some parts of the data collected for the study will be looked at by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All information which is collected about you during the course of the research will be kept **strictly confidential**, stored in a secure and locked office. Any information about you which leaves the hospital will have your name and address removed (anonymised) and a unique code will be used so that you cannot be recognised from it.

Your personal data (address, telephone number) will be kept for 6 to 12 months after the end of the study so that we are able to contact you about the findings of the study and future related work (unless you advise us that you do not wish to be contacted). All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team will have access to your personal data.

Although what you say in the focus group is confidential, should you disclose anything to us which we feel puts you or anyone else at any risk, we may feel it necessary to report this to the appropriate persons.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw then the information collected so far cannot be erased and this information may still be used in the project analysis.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will not be notified of your participation in this study.

What will happen to the results of the research study?

The results of this phase of the research will be used to assess the feasibility of doing a study of excision margins and radiotherapy for SCC in the future. This research will be incorporated into a chapter of the researcher's PhD thesis which will eventually be accessible via the University of Nottingham's on-line thesis repository and may also be published in a peer-reviewed journal or presented at a dermatology conference. You will not be identified in any report or publication resulting form this work.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the National Institute for Health Research as part of a programme grant award (RP-PG-0407-10177) awarded to the Centre of Evidence Based Dermatology.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Coventry and Warwickshire Research Ethics Committee Proportionate Review Sub-Committee.

Further information and contact details

Further information can be obtained from the Centre of Evidence Based Dermatology website:
www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/research/nihrprogrammegrant/skincancer.aspx

Contact: Dr Louise Lansbury (Research Associate)
Tel: 0115 8468721
E-mail: Louise.Lansbury@nottingham.ac.uk

Chief Investigator: Dr Fiona Bath-Hextall (Reader and Associate Professor of Evidence Based Healthcare)
Tel: 0115 8230883

Address: Centre of Evidence Based Dermatology, University of Nottingham, King's Meadow Campus, Lenton Lane, Nottingham NG7 2NR

APPENDIX 6

Questionnaire – feasibility study

Participant Questionnaire

Introduction

Outline of the study

Most squamous cell carcinomas (SCCs) are cut out by a skin surgeon who takes a margin of skin around it which looks normal. The aim is to ensure that all the cancer has been removed whilst maintaining function and the cosmetic appearance of the treated area. Based on the evidence we have available to us at the moment, the British Association of Dermatologists currently recommends that squamous cell cancers that appear to be at low risk of coming back are cut out with a 4mm margin of normal-looking skin around them, and that those cancers which have features making them more likely to come back after treatment are cut out with a 6mm or larger margin. However, there is real uncertainty whether taking a larger margin of apparently normal skin when the cancer is cut out decreases the risk of recurrence.

In addition, some patients receive additional radiotherapy after they have had their SCC cut out, for example those in whom there may be some cancer cells seen around the nerves when it is examined under the microscope, or those in whom there is doubt that all the tumour has been cut out. However, we don't know whether giving radiotherapy after surgery benefits patients in terms of the tumour coming back and longer term survival, nor whether there is group of patients with certain types of SCCs which may benefit particularly from having this extra radiotherapy.

In the study we are proposing, patients whose cancer is considered by their doctor to have features which make it more likely to recur (such as being greater than 2cm in its largest dimension, or invading deeply into the skin, or which are located on the ear or lip), will initially be randomised to have their SCC removed with EITHER:

a) a 6mm margin of normal looking skin around it

OR

b) a 10mm margin of normal looking skin around it (See pictures)

Following surgical excision of their SCC, **some** people whose SCCs have certain additional high-risk features would then be eligible to take part in the second stage of the study, this time being randomised to receive EITHER:

a) additional radiotherapy to the local area

OR

b) NO additional radiotherapy.

The radiotherapy will be given by a clinical oncologist who has expertise in the use of radiotherapy for skin cancer and will require that the patient visits the hospital as required according to the treatment schedule so that the radiotherapy can be given. Not everyone who takes part in the first phase of the trial comparing excision margins will be eligible to be randomised into this second radiotherapy phase if their SCC lacks the characteristics in which we are interested.

All participants will be followed up for 5 years to check that their cancer has not come back, regardless of whether they are involved in just the first stage of the study or in both stages.

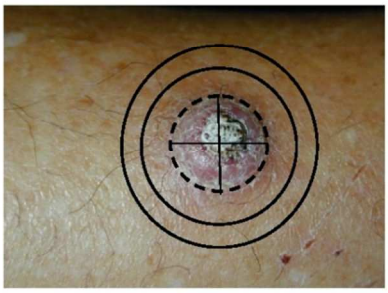
The study would be 'randomised', which means that a computer would assign participants to have their skin cancer cut out with either a 6mm or 10mm margin, and if eligible for the second phase, to either receive additional radiotherapy or no additional radiotherapy. This means that participants have an equal chance of having a 6mm margin and an equal chance of having a 10mm margin, and if applicable, an equal chance of receiving radiotherapy and an equal chance of not receiving radiotherapy. No-one involved in their care would know in advance which treatment participants were going to have. This method produces the fairest results.

If you have any questions about this work or there something you would like clarifying, please contact the lead researcher who will be happy to talk to you:

Dr Louise Lansbury
Centre of Evidence Based Dermatology
Kings Meadow Campus,
University of Nottingham
Nottingham
NG7 2NR

Telephone 0115 8468721
E-mail: Louise.Lansbury@nottingham.ac.uk

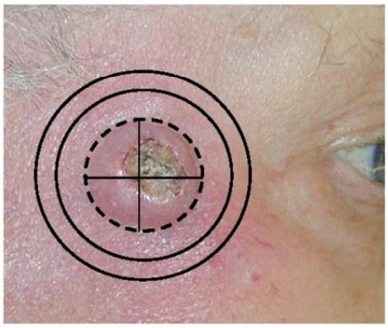
An example of a 2cm forearm SCC (as outlined by dashed line), and the two excision margins which participants could be randomised to: 6mm (inner solid line) and 10mm (outer solid line).



6mm

10mm

An example of a 2cm SCC with 6mm (inner solid line) and 10mm (outer solid line) margin of normal-looking skin – temple



Initials:.....
DOB:.....
Participant code:.....

Questionnaire

Please note that we are only seeking your opinions: we are not asking you to take part in the proposed trial itself.

1 - How willing would you be to be randomised into each stage of the proposed trial?

	Both stages	***First stage only*** (6mm versus 10mm margin)	***Second stage only*** (extra radiotherapy versus No radiotherapy)
Definitely YES			
Probably YES			
NOT SURE			
Probably NOT			
Definitely NOT			

2 – We would like to find out what **barriers** would prevent patients from being willing to participate in this study. Please explain any reasons why you have responded in this way (no matter how trivial you may think these reasons are) [For example, some of the following may be concerns you have thought of: *having radiotherapy; cosmetic appearance; time of extra visits to hospital; cost of extra visits (transport, parking); transport logistics; carer concerns (time off work, commitment, financial); issues around the trial itself);* or you may have thought of other things which would prevent your participation in such a study]

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3 Do you have **PREFERENCE** for one of the treatments over the other?

a) SCC cut-out with a 6mm margin versus 10mm margin of normal looking-skin?

Please TICK one box only:

STRONG preference	SLIGHT preference	NO preference

Initials:……
DOB:……
Participant code:……

If you have ticked that you have a STRONG PREFERENCE for 1 of the treatments over the other, please state WHICH treatment you would prefer if you had a choice.

Preferred treatment: ……..

Please outline the reasons why you have a strong preference for this treatment:
……
……
……
……..……

b) SCC cut-out and then receive extra radiotherapy to the area, or SCC cut-out with NO additional radiotherapy?

Please TICK one box only:

STRONG preference	SLIGHT preference	NO preference

If you have ticked that you have a STRONG PREFERENCE for 1 of the treatments over the other, please state WHICH treatment you would prefer if you had a choice.

Preferred treatment: ……..

Please outline the reasons why you have a strong preference for this treatment:
……
……
……
……..

4 – From your own personal point of view, which of the following outcomes after treatment do you consider to be the most important (Tick one only)?

Good cosmetic appearance of the treated area …….
Getting rid of the cancer ……..
Maintenance of function in the area ……
Decreasing the risk of the cancer coming back ……..

Initials:.....
DOB:.....
Participant code:.....

5 - Are there any other comments that you would like to make relating to this study?

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Demographic data

To help analyse our results, we would like to collect some information about you.
All data collected will be anonymous and will only be used for the purposes of this study.
You will not be identifiable from any of the information you provide.

Age: .....

Male/female (please delete as appropriate)

Work status: Please tick one
Full/part-time employed .....
Self-employed.....
Retired.....
Unemployed.....
Not working due to health.....
Student.....

Education level attained:
Postgraduate/professional qualifications .....
Graduate .....
'A' level .....
'O' level/GCSE .....
No formal qualifications .....

Initials:……
DOB:……
Participant code:……

Focus Group

Would you be interested in taking part in a focus group with 4 or 5 other people to discuss in more detail issues relating to the proposed trial and other more general questions about taking part in clinical trials?

Definitely YES	
Maybe	
NO	

If you have answered 'yes' or 'maybe', a member of the research team will contact you with further details of the focus group.

Results Summary

Would you be interested in receiving a summary of the results of this research when we have analysed the data?

YES/NO

Helping in the future

Would you be interested in reviewing and commenting on information resources which we will be developing and will give to people who take part in our proposed trial, or to other patients who develop this type of skin cancer?

YES/NO

MANY THANKS FOR COMPLETING THIS QUESTIONNAIRE – YOUR RESPONSES ARE VERY VALUABLE TO US. PLEASE USE THE ENCLOSED PRE-PAID ENVELOPE TO RETURN YOUR COMPLETED QUESTIONNAIRE WITHIN 14 DAYS OF RECEIPT TO:

Dr Louise Lansbury
Centre of Evidence Based Dermatology
Kings Meadow Campus
University of Nottingham
Nottingham NG7 2NR

APPENDIX 7

Consent form for focus group

Centre of Evidence Based Dermatology
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR

CONSENT FORM
(Final version 1.0: date 17/01/2013)

Title of Study: Participant acceptability of a proposed future skin cancer trial

REC ref: 13/WM/0051

Name of Researcher: Dr Louise Lansbury

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 1.0 dated.17 January 2013 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand that the focus group will be recorded and that anonymous direct quotes from the focus group may be used in the study reports. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

2 copies: 1 for participant and 1 for the project notes

APPENDIX 8

Focus group schedule

The University of Nottingham

Centre of Dermatology Evidence Based

Focus group schedule

- Welcome and introductions
- Purpose of the focus group
  - Main focus will be on issues that could affect willingness to take part in a skin cancer trial
  - Confidentiality, audio recording, procedure
- How the focus group will operate
  - Open discussion
  - Focussing in on certain questions
  - Finishing with suggestions for increasing recruitment
- Consent forms signed

Initial approach

"What do you know about clinical research in general?"

Probe:

- *Why is it done?*
- *Is it important?*
- *Who benefits? – participants/researchers/clinicians/others*
- *Advantages/disadvantages of taking part*
- *Understanding of the process/randomisation*
- *Concerns about trials/randomisation*

Clinical research in cancer

"What do you think about people with cancer taking part in clinical research?"

Probe:

- *Advantages/disadvantages*
- *What sort of barriers may prevent people with cancer wanting to take part?*
- *Are there some cancers/groups of patients who may be less willing to take part*

Clinical Research in skin cancer

"Going back to when you received your diagnosis of skin cancer, how do you think you would have felt if asked to take part in a trial in which your cancer could be cut out with either a 6mm or a 10mm margin of normal looking skin?"

Probe:

- *Concerns*
- *Effect of site of cancer on decision*
- *Any perceived advantages/benefits in joining the trial*
- *Any perceived disadvantages/reservations*
- *Easy or hard decision to take part*

"Supposing the suggested trial had an additional component, in which some of the people taking part were identified by a team of specialists as having particular skin cancers which would be eligible to be randomised to receive either additional radiotherapy or no additional radiotherapy at the site of the cancer. How would you feel about this?"

Probe:

- *Concerns/factors which could influence willingness to take part*
- *Perceived advantages/disadvantages*

Understanding of skin cancer

"When you were first told that you had skin cancer, what were your main sources of information to help you understand your condition?"

Probe:

- *Dermatologist/other health professional*
- *Information leaflet from clinic*
- *Family/friends*
- *Internet/books*

"Did you feel adequately informed about your condition, or were there some aspects about which you would like to have had a better understanding?

Probe:

- *Type of skin cancer (non-melanoma versus melanoma)*
- *Understanding treatment*
- *Recognising similar skin lesions in the future*

Could the provision of information have been improved, and if so, in what way?

Probe:

- *Format of materials/*
- *Comprehensibility*
- *Time spent by staff on explanation*

Treatment

"Thinking back to the treatment you had, what were your main concerns about the treatment itself and its outcome?"

Probe:

- *Clearance*
- *Cosmetic*
- *Recurrence*
- *Functional impairment*
- *Social/inconvenience*

"Can you relate any positive, or negative experiences associated with your treatment?"

Closing questions

"From the potential participant's point of view, what do you think is the most important issue we need to consider when developing our skin cancer trial?"

Summary of points emerging

Thank you