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Surgery versus 5% Imiquimod for Nodular and Superficial basal-cell carcinoma: five year results of the SINS randomised controlled trial

Short title: SINS RCT in BCC: five year results

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Keywords

Basal cell carcinoma; BCC; imiquimod; surgery; non-inferiority study; randomised controlled trial

Abbreviations

BCC = basal cell carcinoma; nBCC = nodular basal cell carcinoma

sBCC = superficial basal cell carcinoma; PDT = photodynamic therapy

RCT = randomised controlled trial

Abstract – 200 words

Main text - 2600 words

Tables - 1

Figures - 1

References - 23

ABSTRACT

Background: We previously reported modest clinical 3-year benefit for topical imiquimod compared with surgery for superficial or nodular basal cell carcinoma (sBCC, nBCC) at low risk sites in our non-inferiority randomised controlled SINS trial. Here we report 5-year data.

Methods: Participants were randomised to imiquimod 5% cream once daily (sBCC, 6 weeks; nBCC, 12 weeks) or excisional surgery (4 mm margin). Primary outcome was clinical absence of initial failure or signs of recurrence at 3 year dermatology review. Five year success was defined as 3 year success plus absence of recurrences identified through hospital, histopathology and general practitioner records.

Results: Of 501 participants randomised, 401 contributed to the modified intention-to-treat analyses at year 3 (primary outcome), 383 (96%) of whom had data at year 5. Five year success rates for imiquimod were 82.5% (170/206) compared to 97.7% (173/177) for surgery (relative risk of imiquimod success 0.84, 95% CI 0.77 to 0.91, $p < 0.001$). These were comparable to year 3 success rates of 83.6% (178/213) and 98.4% (185/188), for imiquimod and surgery, respectively. Most imiquimod treatment failures occurred in year one.

Interpretation: Although surgery is clearly superior to imiquimod, this study shows sustained benefit for lesions that respond early to topical imiquimod.

INTRODUCTION

Basal cell carcinomas (BCCs) are the commonest form of human cancer with an estimated 1 million cases diagnosed each year in the US (Prieto-Granada and Rodriguez-Waitkus, 2015). The incidence of BCC is rising by around 10% each year (Karagas and Greenberg, 1995) in white populations such as those living in Australia (Perera et al., 2015), yet poor registration of BCC makes it difficult to compare estimates across the world (Hay et al., 2014). A range of genetic factors have been associated with BCC and recurrent BCC (Madan et al., 2010), but unlike cutaneous squamous cell carcinoma, the relationship between sun exposure patterns and different types of BCC is still unclear. Although deaths from BCC are rare (Boyers et al., 2014), considerable morbidity may result due to the local aggressive nature of BCC and BCC recurrences (Hollestein et al., 2014). Trends in ageing populations means that supply of appropriate treatment such as excisional surgery may be stretched in State healthcare systems such as the UK National Health Service, and it has been estimated that the number of cases presenting to dermatologists will increase by 50% by 2030 (Madan et al., 2010). Such a trend has resulted in guidance for more family practitioners to provide treatment for low risk lesions in the community (Fremlin et al., 2016). Although excisional surgery remains the gold standard for most common types of BCC, a range of non-surgical approaches are available including photodynamic therapy (Wang et al., 2015), topical imiquimod cream, topical 5-fluorouracil, and topical ingenol (Clark et al., 2014). We previously published the 3 year results of an independent comparison of topical imiquimod versus excisional surgery for the treatment of low risk superficial and nodular BCC in the SINS trial (Bath-Hextall et al., 2014). Although the topical imiquimod response rate of 84%, compared with 98% for surgery, failed to meet our pre-defined non-inferiority margin of a relative risk of 0.87, it nevertheless offered a potentially useful treatment option that may be suitable for first treatment of low risk BCC in the community, with recurrences being dealt

with by specialists through more sophisticated treatments such as excisional surgery or Mohs micrographic surgery . One major concern with non-surgical topical treatments is that the visible superficial portions of a BCC may appear to clear on early clinical inspection, only for invasive BCC to emerge some years after treatment. We previously called this phenomenon “submarine lesions” (Williams HC, 2014). There are additional concerns that some forms of topical chemotherapy such as 5-fluorouracil, may alter the biological behaviour of BCC from a simple to a more difficult to treat lesion such as a morphoeic BCC (Xiong et al., 2014). For these reasons, it is important to follow up BCC trial participants for at least 5 years. Here, we report the 5 year follow-up of the SINS study participants using histopathology and healthcare records.

RESULTS

Participants were recruited between June 19, 2003, and February 22, 2007, with 3 year follow-up in clinic from June 26, 2006, to May 26, 2010, and 5 year follow-up of hospital, GP and histopathology records completed in 2012. Participant characteristics have been published in the previous 3 year data report (Bath-Hextall et al., 2014). Participant flow from randomisation to 5 years is shown in the figure. A total of 18 patients did not have usable data at year 5. In the imiquimod group, three had died and we could not determine if recurrence had occurred in four (three not sure from records and one visit not done). In the surgery group, six had died and we could not determine if recurrence had occurred in five (three not sure, one visit done too early and one not done).

Recurrences recorded at 5 years compared with 3 years are shown in the table, broken down into early treatment failures and later recurrences as recommended in previous correspondence to our article (Bassukas and Gaitanis, 2014). Additional recurrences between 3 and 5 years were small with one additional recurrence for a superficial BCC treated with imiquimod and one for surgery. Histological subtype was unknown for the one recurrence on topical imiquimod (patient was treated with cryotherapy) and was recorded as superficial basal cell carcinoma for the one recurrence on surgery.

DISCUSSION

The 5 year follow-up data from the SINS study do not suggest a progressive rise in BCC recurrences between years 3 to 5, nor do they suggest that recurrences in the imiquimod group were difficult to spot, or that they had transformed from superficial to morpheaic forms as is the concern with some other topical treatments such as PDT (Bernabo et al., 2016; Xiong et al., 2014). Most treatment failures with topical imiquimod occurred in the first year of treatment, a finding that throws light on the possible mechanisms of topical immunotherapy for skin cancer - suggesting that once an immunological response has occurred, such a response is sustained. The new data presented in this report do not lend any support to concerns of “submarine” lesions emerging on the skin surface years after early apparent clinical benefit of topical treatment. The absolute response rate for topical imiquimod of 83% at 5 years, whilst clearly inferior to the 98% for excisional surgery for low risk BCC, might still represent a clinically useful treatment modality since a cream treatment can be carried out in a primary care setting and some patients may also prefer the option of a cream rather than surgery.

Clark et al. (2014) summarise 29 RCTs and 7 systematic reviews of comparative effectiveness of treatments for BCC published up to August 2013 from four databases and cite photodynamic therapy (PDT), topical imiquimod, cryotherapy and topical 5-fluorouracil as suitable treatment options for primary low-risk lesions. They found insufficient evidence to make recommendations on the use of topical ingenol mebutate, solasodine glycoalkaloids, IFN- α or intralesional 5-fluorouracil, and no RCT evidence on electrodesiccation and curettage, which is a commonly used procedure for low risk BCC. Wang et al. (2015) in their systematic review of RCTs of PDT for BCC published up to October 2013 found eight studies, two of which included a comparison with surgical excision with 5 year follow up

data. The first of these was an RCT by Rhodes et al. (2007) that compared topical methyl aminolevulinate photodynamic therapy versus simple excision surgery for primary nodular BCC in 97 patients. They estimated a sustained lesion complete response rate of 76% (95% CI, 59%-87%) and 96% (95% CI, 84%-99%) for PDT and surgery respectively at 5 years. Inspection of the time to event analysis in that study showed a steady increase in recurrences throughout the 5 year follow-up, rather than a pattern of early treatment failures and low recurrences thereafter as seen for topical imiquimod in this SINS study. The other RCT that evaluated fractionated 20% 5-aminolevulinic acid (ALA)-PDT with prior partial debulking versus surgical excision in nodular BCC in 151 patients with nodular BCC (Roozeboom et al., 2013), showed a cumulative probability of recurrence of 30.7% (95% CI 21.5%-42.6%) for ALA-PDT and 2.3% (95% CI 0.6%-8.8%) for surgical excision, but with much lower rates of recurrence for tumours ≤ 0.7 mm thick. Their Kaplan-Meier plot suggested a steeper slope for recurrences over years 1 to 3. Another systematic review of interventions for superficial BCC in 2012 found pooled estimates from 23 randomized and non-randomized studies of 87.3% for imiquimod (95% CI 84–91%) and 84.0% for PDT (95% CI 78–90%) (Roozeboom et al., 2012). A subsequently published non-inferiority RCT performed a head to head comparison between topical 5-FU, topical 5% imiquimod and methyl aminolevulinate-photodynamic therapy (MAL-PDT) in 601 patients with superficial BCC, followed up for 1 and 3 years (Arits et al., 2013; Roozeboom et al., 2016). They found that tumor-free survival at 3 years post-treatment was 58.0% for MAL-PDT (95% confidence interval [CI] = 47.8-66.9), 68.2% for topical fluorouracil (95% CI = 58.1-76.3) and 79.7% for imiquimod (95% CI = 71.6-85.7), with clear evidence that topical imiquimod was superior to MAL-PDT (treatment failure hazard ratio for imiquimod compared with MAL-PDT was 0.50, 95% CI = 0.33-0.76, P = 0.001). Tumour thickness does not seem to predict treatment failure for topical imiquimod, PDT or topical 5-fluorouracil (Roozeboom et al.,

2015). We have been unable to identify any further trials comparing topical imiquimod versus other active therapies for the treatment of low risk nodular or superficial BCC, and none with 5 years follow-up. A review has shown that radiotherapy also offers comparable cure rates (Cho et al, 2014) and good cosmetic outcomes, but only two RCTs were included in that review.

Strengths of this study include the large size and pragmatic design that included a wide range of patients who might be considered for such treatment in primary care. Observer bias is unlikely given that 5 year results were collected from a range of routine sources in which a vested interest in the direction of the results would be unlikely. Analysis at 5 years used an intention to treat approach and losses to follow up between years 3 to 5 were relatively small. Study limitations include the fact that we used imiquimod 7 days a week, rather than the current licensed 5 days a week. Recurrences at 5 years were identified by checks on notes and histopathology records rather than direct clinical examination of participants, so it is possible that some less noticeable recurrences might have been missed, especially as follow-up between 3 to 5 years following treatment is likely to have been done in the community by general practitioners who may be less skilled in identifying possible recurrences. On the other hand, it is possible that patients and their doctors might have demonstrated increased vigilance in looking out for recurrences given that so much attention was paid to the “study lesion” for the first 3 years of the study, and given that topical imiquimod was a “new” treatment at the time of the study. Furthermore, such potential missed recurrences are likely to be similar for both treatment groups. Some of the surgeons delivering care in the SINS study were trained in advanced surgery and therefore not typical of secondary care or primary care. In terms of external validity, it is possible that the study favoured slightly younger people with BCC who were more mobile than some of the older and more frail patients who

declined to participate, and it is also possible that those entering the study were motivated about the prospect of getting topical imiquimod which was not licensed for BCC at the start of the study.

Although the SINS study has shown that 3 and 5 year results for topical imiquimod for low risk superficial and nodular BCC are clearly inferior to excisional surgery, the overall success rate of 82.5% at 5 years still represents a useful clinical response, especially as most treatment failures are identified early and long-term responses seem to be maintained. Application site reactions, reported in more detail in the 3 year analysis included itching and weeping, were rarely severe enough to withdraw from treatment. Recurrences of low risk BCC treated with topical imiquimod did not appear to be difficult to treat. A possible future strategy to deal with the epidemic of BCC might be to treat low risk BCC in the community using imiquimod and to deal with recurrences surgically. Suitably informed patients could make their own choice about the use of imiquimod and other non-surgical treatment modalities. The SINS study now provides valuable data to inform such shared decision making that might be delivered to patients by video-based educational materials (Love et al., 2016).

Many people with BCC are elderly but as seen in this study only a small number had died before the 5 year data was collected. Future comparative studies should include 5 year follow up data, a surgical trial arm to allow standardised comparisons with other studies and a presentation of overall data on early treatment failures and late recurrences (Bassukas and Gaitanis, 2014).

METHODS

These have been described in full in our previous publications (Bath-Hextall et al., 2014, Ozolins et al., 2010). Briefly, the SINS study is a multi-centre, parallel group pragmatic non-inferiority randomised trial to see if imiquimod is non-inferior to surgery. Eligible participants had histologically confirmed primary, previously untreated, nodular or superficial BCCs not occurring in sites at high risk for subclinical tumour spread which include the nose, ear, eyelid, eyebrow, and temple. Those with morphoeic or recurrent BCCs and patients with Gorlin syndrome were excluded. Participants were randomised to imiquimod 5% cream once daily for 6 (superficial) or 12 (nodular) weeks, or surgical excision with a 4 mm margin. Participants were initially recruited from three dermatology secondary care centres, with an additional nine centres engaged to boost recruitment. Written informed consent was provided by all participants. Those consented were allocated to treatment group via remote randomisation by The Trent Research and Development Support Unit using block randomisation and stratifying by centre and BCC type. The list was concealed from investigators. Masking of participants was not possible due to the nature of the interventions and masking of outcome assessors was only partially possible because of surgical scars. The primary outcome previously reported was the proportion of participants with clinical evidence of success, (defined as neither initial treatment failure nor signs of local recurrence when reviewed at 3 years by consultant dermatologists). Secondary outcomes included clinical success at 1, 2 and 5 years; time to first failure; cost effectiveness, cosmetic appearance of lesion site assessed by participant and dermatologist assessor; pain during treatment and in the 16 weeks follow up; and number of days participants experienced moderate/severe pain during treatment and 16 week follow up. The full rationale for the sample size is reported in the previous paper and study protocol (Bath-Hextall et al., 2014,

Ozolins et al., 2010), but due to recruitment difficulties and following sample size reassessment, recruitment was stopped at 501 participants. The non-inferiority margin based on these figures is a relative risk of 0.87 (lower boundary of a 98% CI for the relative difference in effect expressed as a relative risk), and only applies to the primary outcome. Data were analysed using Stata version 13.1 according to the pre-specified analysis plan. A modified intention-to-treat analysis was conducted on the full dataset (all randomised participants with a histologically confirmed BCC lesion, who met the inclusion/exclusion criteria, received at least one application of imiquimod or surgery and for whom the outcome of interest was available) for all outcome measures, and a per-protocol analysis was also conducted for the primary outcome at 3 years. All analyses were adjusted for centre, BCC type (superficial or nodular), size and site of tumour, and immunosuppression at baseline. Poisson regression with a robust error variance was used to estimate the treatment effect as a relative risk. Treatment success at 5 years was defined as those achieving success at the primary outcome assessment at 3 years plus absence of further recurrences at 5 years. Long term adverse event data were not collected, but deaths were recorded. The 5 year BCC recurrence data for those participants who were included in the 3 year primary outcome analysis were retrieved from at least one and more often than not all of the following three sources: (i) hospital histopathology records from each centre, follow-up of (ii) general practitioner and (iii) hospital records. The only data that were recorded were whether the trial participant had a recurrence of the BCC originally treated, with the date of recurrence, and if relevant the date and cause of death. No additional data were recorded at 5 years, apart from explanatory notes, particularly where evidence were not clear.

Role of funding source

The study was funded by Cancer Research UK. Meda (previously 3M) donated 5% imiquimod cream free of charge. Funders did not play any role in the study design, collection of data, analysis or interpretation of data, nor did they contribute to the writing of this report or the decision to submit the paper for publication.

Trial registration

This trial is registered as an International Standard Randomised Controlled Trial (ISRCTN48755084), and with ClinicalTrials.gov, number NCT00066872.

Declaration of interests

We declare that we have no conflict of interest.

Acknowledgments

We would like to thank the patients who agreed to participate in this study, and all those who helped with running the study. The study was financed by Cancer Research UK. We would also like to thank Meda (previously 3M) for donating 5% imiquimod cream free of charge. Thanks also to Dr John English for helping with the blinded assessment of cosmetic appearance and to Mr Jack Tweed (patient/public member) for his suggestions on initial study design. We also thank Dr. Natasha Rogers for help in editing the manuscript.

Investigators: Please see online appendix

Figure Legend

Figure: CONSORT Flow Diagram for SINS 5-year data

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Table: Success at 3 and 5 years – intention to treat analysis

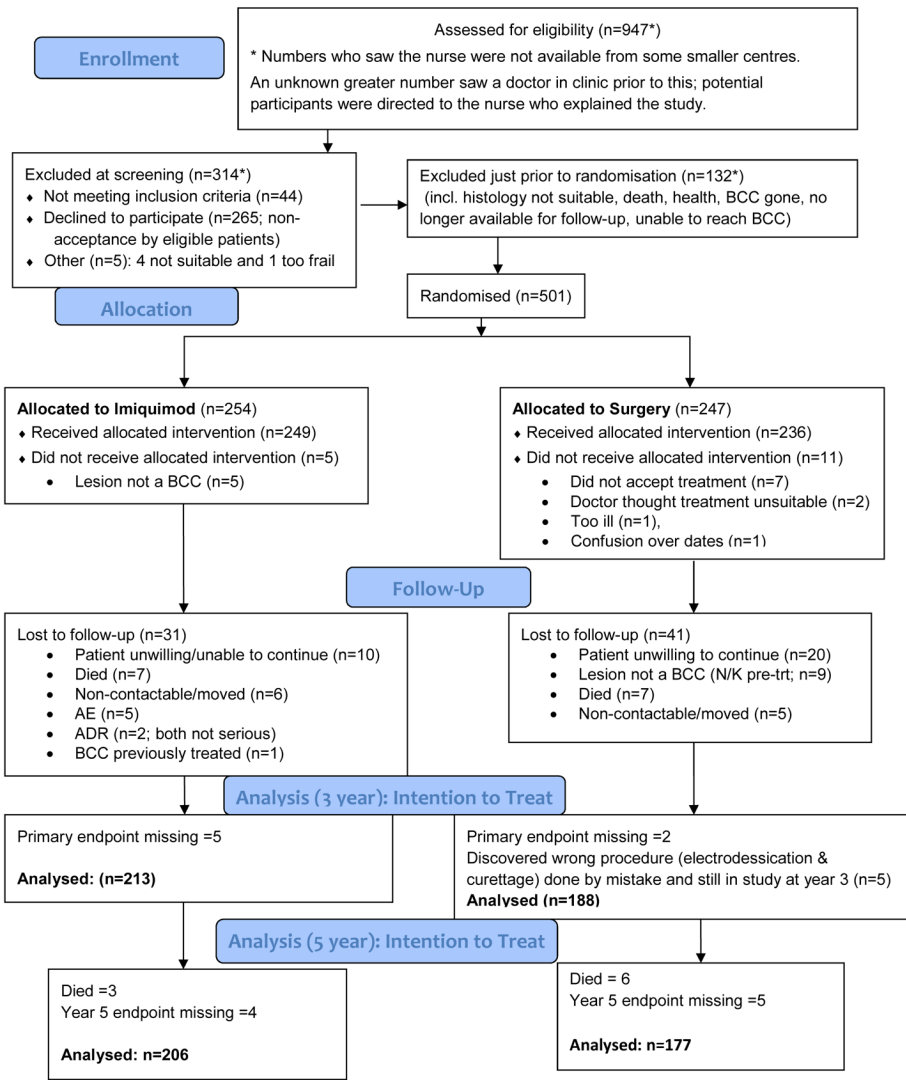
Time	BCC type	Success Imiquimod			Success Surgery			Difference S-I (98% CI) (%)	relative risk with 98% CI (I relative to S)	p-value from LRT
		n (%)	Early failures	Later recurrence	n (%)	Early failures	Later recurrence			
3 years	Superficial	97/114 (85.1)	10	7	96/98 (98.0)	1	1	12.9 (4.4, 21.3)		
	Nodular	81/99 (81.8)	15	3	89/90 (98.9)	1	0	17.1 (7.7, 26.4)		
	All	178/213 (83.6)	25	10	185/188 (98.4)	2	1	14.8 (8.6, 21.1)	0.84 (0.78 ^a , 0.91)	<0.001
5 years	Superficial	93/111 (83.8)	10	8 (recurrences between year 3 and 5 = 1)	91/94 (96.8)	1	2 (recurrences between year 3 and 5 = 1)	13.0 (3.9, 22.2)		
	Nodular	77/95 (81.1)	15	3 (recurrences between year 3 and 5 = nil)	82/83 (98.8)	1	0 (none between year 3 and 5)	17.7 (8.0, 27.5)		
	All	170/206 (82.5)	25	11 (recurrences between year 3 and 5 = 1)	173/177 (97.7)	2	2 (recurrences between year 3 and 5 = 1)	15.2 (8.5, 21.9)	0.84 (0.77 ^a , 0.91)	<0.001

CI = confidence interval; LRT=likelihood ratio test

^a Imiquimod (I) deemed to be non-inferior to surgery (S) if this lower limit >0.87

Relative risk analysis covariates: centre, tumour type (nodular or superficial), tumour size, tumour site and immunosuppression

Figure: CONSORT Flow Diagram for SINS 5-year data



Online appendix: Centres, investigators and participant recruitment for the SINS trial.

Centre	Principal Investigator	SINS nurses, network research nurses and other main support staff	Hospitals included under centre	Number randomised
Solihull	Dr Irshad Zaki	SINS nurse: Beryl Cunningham	Solihull Hospital	135
Chesterfield	Dr Graham Colver	SINS nurses: Gloria Kemeny and Sam Annasamy. Network cover: Helen Beadle	Chesterfield Royal	127
QMC	Dr William Perkins	SINS nurse: Jo Llewellyn; Pharmacy (Sheila Hodgson and staff: packing, labelling, testing and distribution); maternity cover: Afsana Zaman.	Queen's Medical Centre, Nottingham	125
KMH	Dr Jan Bong	SINS nurse: Jo Llewellyn. Maternity cover: Dominic Nash	King's Mill Hospital, Sutton in Ashfield	62
Lanarkshire	Dr Girish Gupta	Linda Callachan, Paula Botham, Margaret Nisbet, June Carr (Cameron), Natalie Singer	Hairmyres; Wishaw; Monklands	17
Barts	Dr Catherine Harwood (prev. Dr Steve Nicholson)	Denise Andrews, Aryana Chopra	St Barts and The London	12
Lincoln	Dr Khalid Hussain	Network staff: Issy Thomas, Annette Hildrith, Karen Metcalf, Ray McDermott, Tania Williamson, Teresa Clarke, Ann Wilson, Andrea Rodger	Lincoln County; Pilgrim, Boston	10
Inverclyde	Dr Clare Fitzsimons (prev. Dr Malcolm Young)	Pamela Eaddy, Sandra Hanlon, Shona McDermott	Inverclyde Royal	6
Birmingham	Dr Camilo Diaz	Kerry Shalders, Agustin Martinclavijo	Birmingham City	3
S.Glasgow	Dr Robert Herd	Kirsty Crozier, Claudia Turley, Emma Moody, Donna McWilliam, Karen Bell.	Victoria; Southern General	2
Liverpool	Dr Graham Sharpe	Linda Gauden	Broadgreen	1
Dorset	Dr Simon Tucker	Karen Hogben, Angela Cox, Barbara Burgess	Dorset County	1
TOTAL				501