See related commentary on pg 539

# Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial

Hywel C. Williams[1], Fiona Bath-Hextall[1,2], Mara Ozolins[1,3], Sarah J. Armstrong[4], Graham B. Colver[5], William Perkins[6] and Paul S.J. Miller[4], on behalf of the Surgery Versus Imiquimod for Nodular and Superficial Basal Cell Carcinoma (SINS) Study Group

We previously reported modest clinical 3-year benefit for topical imiquimod compared with surgery for superficial or nodular basal cell carcinoma at low-risk sites in our noninferiority randomized controlled SINS trial. Here we report 5-year data. Participants were randomized to imiquimod 5% cream once daily (superficial basal cell carcinoma, 6 weeks; nodular basal cell carcinoma, 12 weeks) or excisional surgery (4-mm margin). The primary outcome was clinical absence of initial failure or signs of recurrence at the 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. Of 501 participants randomized, 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 with 97.7% (173/177) for surgery (relative risk of imiquimod success = 0.84, 95% confidence interval = 0.77–0.91, $P < 0.001$). 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 1. Although surgery is clearly superior to imiquimod, this study shows sustained benefit for lesions that respond early to topical imiquimod.

*Journal of Investigative Dermatology* (2017) **137,** 614–619; doi:10.1016/j.jid.2016.10.019

## INTRODUCTION

Basal cell carcinomas (BCCs) are the most common form of human cancer, with an estimated 1 million cases diagnosed each year in the United States (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 because of the local aggressive nature of BCC and BCC recurrences (Hollestein et al., 2014). Trends toward aging populations mean that the supply of appropriate treatment such as excisional surgery may be stretched in state-run health care systems such as the UK National Health Service, and it has been estimated that the number of patients 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 criterion standard for most common types of BCC, a range of nonsurgical approaches is 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 predefined noninferiority 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 nonsurgical topical treatments is that the visible superficial portions of a

[1]*Centre for Evidence Based Dermatology, University of Nottingham, Nottingham, UK;* [2]*School of Health Sciences University of Nottingham, Nottingham, UK;* [3]*NIHR Nottingham Hearing Biomedical Research Unit, University of Nottingham, Nottingham, UK;* [4]*School of Medicine, University of Nottingham, Nottingham, UK;* [5]*Department of Dermatology, Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield, UK; and* [6]*Department of Dermatology, Nottingham University Hospitals NHS Trust, Nottingham, UK*

*Correspondence: Hywel C. Williams, Centre for Evidence Based Dermatology, University of Nottingham, Nottingham, NG7 2NR, UK. E-mail: Hywel.williams@nottingham.ac.uk*

*Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; PDT, photodynamic therapy; RCT, randomized controlled trial*

*Received 27 August 2016; revised 27 September 2016; accepted 6 October 2016; corrected proof published online 5 December 2016*

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, 2014). There are additional concerns that some forms of topical chemotherapy, such as 5-fluorouracil, may alter the biological behavior 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 results of the SINS study participants using histopathology and health care records.

## RESULTS

Participants were recruited between June 19, 2003, and February 22, 2007, with 3-year follow-up at the clinic from June 26, 2006, to May 26, 2010, and 5-year follow-up of hospital, general practitioner, and histopathology records completed in 2012. Participant characteristics have been published in the previous 3-year data reports (Bath-Hextall et al., 2014). Participant flow from randomization to 5 years is shown in the Figure 1. 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 Table 1, 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 BCC 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 and 5, nor do they suggest that recurrences in the imiquimod group were difficult to spot or that they had transformed from superficial to morphoeic forms, as is the concern with some other topical treatments such as photodynamic therapy (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, although clearly inferior to the 98% for excisional surgery for low-risk BCC, might still represent a clinically useful treatment modality, because 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) summarized 29 randomized controlled trials (RCTs) and seven systematic reviews of the comparative effectiveness of treatments for BCC published through August 2013 from four databases and cite 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 through 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% confidence interval [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, which evaluated fractionated 20% 5-aminolevulinic acid−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 5-aminolevulinic acid−PDT and 2.3% (95% CI = 0.6−8.8%) for surgical excision, but much lower rates of recurrence for tumors at or less than 0.7 mm thick. Their Kaplan-Meir plot suggested a steeper slope for recurrences over years 1−3. Another systematic review of interventions for superficial BCC in 2012 found pooled estimates from 23 randomized and nonrandomized 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 noninferiority RCT performed a head-to-head comparison between topical 5-fluorouracil, topical 5% imiquimod, and methyl aminolevulinate-photodynamic therapy 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 methyl aminolevulinate-PDT (95% 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 methyl aminolevulinate-PDT (treatment failure hazard ratio for imiquimod compared with methyl aminolevulinate-PDT was 0.50, 95% CI = 0.33−0.76, $P$ = 0.001). Tumor 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

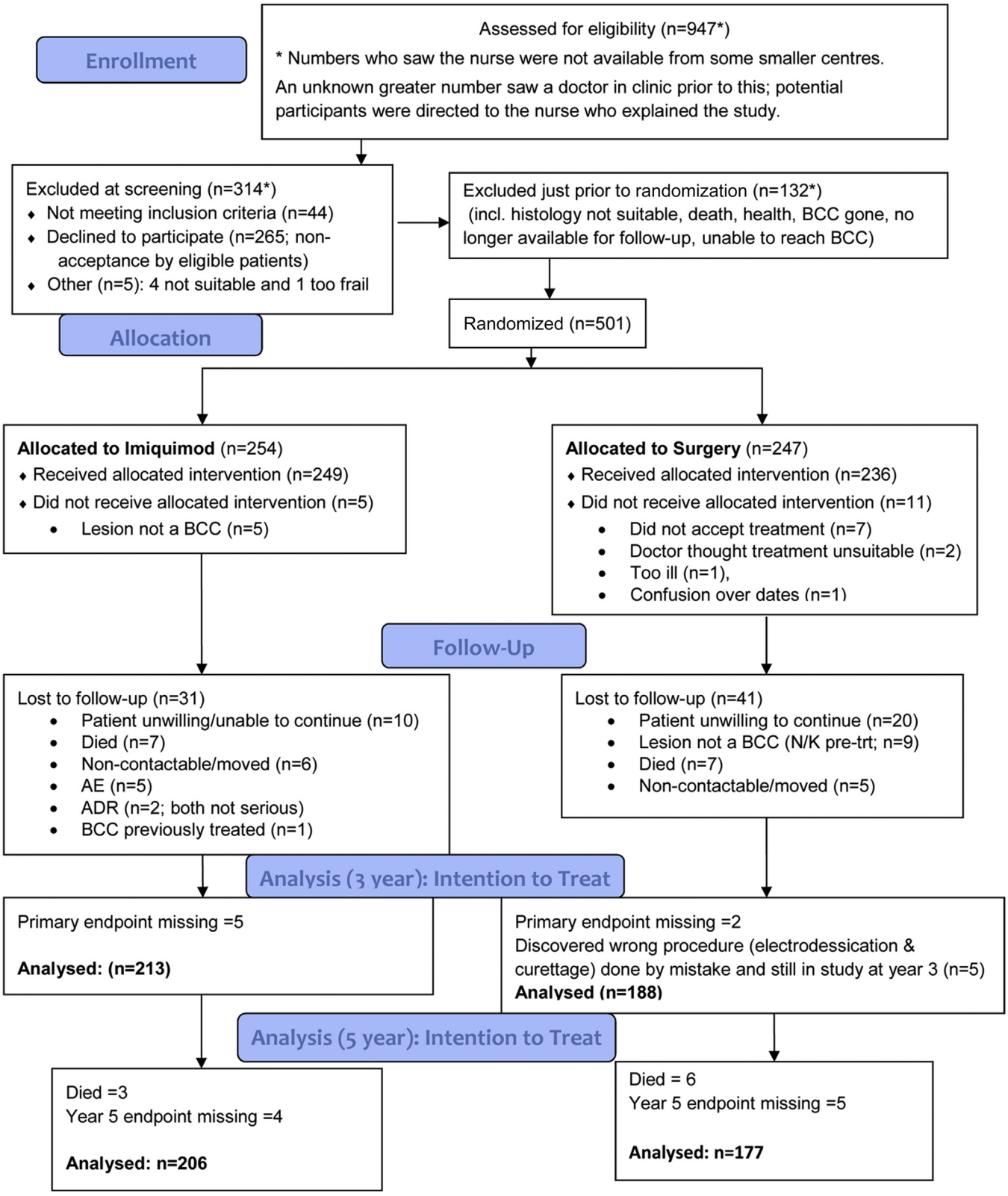


**Figure 1. Flow of participants in the SINS trial from randomization until year 5.** CONSORT flow diagram for SINS 5-year data.

superficial BCC, and none with 5 years of 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 a 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

**Table 1. Success at 3 and 5 years: intention to treat analysis**

| Time | BCC Type | Success Imiquimod n (%) | Early Failures | Later Recurrence | Success Surgery n (%) | Early Failures | Later Recurrence | Difference S − I, % (98% CI) | Relative Risk[1] of I to S (98% CI) | *P*-Value from LRT |
|---|---|---|---|---|---|---|---|---|---|---|
| 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[2]–0.91) | <0.001 |
| 5 years | Superficial | 93/111 (83.8) | 10 | 8 (recurrences between years 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 years 3 and 5 = 0) | 82/83 (98.8) | 1 | 0 (none between years 3 and 5) | 17.7 (8.0–27.5) | — | — |
| | All | 170/206 (82.5) | 25 | 11 (recurrences between years 3 and 5 = 1) | 173/177 (97.7) | 2 | 2 (recurrences between years 3 and 5 = 1) | 15.2 (8.5–21.9) | 0.84 (0.77[2]–0.91) | <0.001 |

Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; I, imiquimod; LRT, likelihood ratio test; S, surgery.
[1]Relative risk analysis covariates: center, tumor type (nodular or superficial), tumor size, tumor site, and immunosuppression.
[2]Imiquimod deemed to be noninferior to surgery if this lower limit was >0.87.

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 and 5 were relatively small. Study limitations include the fact that we used imiquimod 7 days a week rather than the currently approved 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 because follow-up at 3–5 years after 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 shown 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 favored 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 approved 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 because 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 but 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 choices about the use of imiquimod and other nonsurgical 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 were collected. Future comparative studies should include 5-year follow-up data, a surgical trial arm to allow standardized comparisons with other studies, and a presentation of overall data on early treatment failures and late recurrences (Bassukas and Gaitanis, 2014).

## MATERIALS AND METHODS

The materials and methods have been described in full in our previous publications (Bath-Hextall et al., 2014, Ozolins et al., 2010). Briefly, the SINS study is a multicenter, parallel-group, pragmatic, noninferiority randomized trial investigating whether imiquimod is noninferior to surgery. Eligible participants had histologically confirmed, primary, previously untreated nodular or superficial BCCs not occurring in sites at high risk for subclinical tumor 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 randomized to receive imiquimod 5% cream once daily for 6 (superficial) or 12 (nodular) weeks or to have surgical excision with a 4-mm margin. Participants were initially recruited from three dermatology secondary care centers, with an additional nine centers engaged to boost recruitment. Written informed consent was provided by all participants. Those who consented were allocated to treatment group via remote randomization by The Trent Research and Development Support Unit using block randomization and stratifying by center and BCC type. The list was concealed from investigators. Masking of participants was not possible because of 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 the lesion site assessed by participant and dermatologist assessor; pain during treatment and in the 16 weeks of follow-up; and number of days participants experienced moderate to severe pain during treatment and 16 the weeks of 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 because of recruitment difficulties and after sample size reassessment, recruitment was stopped at 501 participants. The noninferiority 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 applies only to the primary outcome.

Data were analyzed using Stata version 13.1 (StataCorp, College Station, TX) according to the prespecified analysis plan. A modified intention-to-treat analysis was conducted on the full dataset (all randomized participants with a histologically confirmed BCC lesion, who met the inclusion/exclusion criteria, who 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 center, BCC type (superficial or nodular), size and site of tumor, 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 center and follow-up of (ii) the 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.

### Trial registration

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

## CONFLICT OF INTEREST

The authors state 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 John English for helping with the blinded assessment of cosmetic appearance and to Jack Tweed (patient/public member) for his suggestions on initial study design. We also thank Natasha Rogers for help in editing the manuscript.

### Disclaimer

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.

## AUTHOR CONTRIBUTIONS

See Supplementary Appendix S1 online for author contributions.

## SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.10.019.

## REFERENCES

Arits AH, Mosterd K, Essers BA, Spoorenberg E, Sommer A, De Rooij MJ, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. Lancet Oncol 2013;14:647–54.

Bassukas ID, Gaitanis G. Basal-cell carcinoma: no response versus relapse. Lancet Oncol 2014;15:e104–5.

Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, Miller PS, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. Lancet Oncol 2014;15:96–105.

Bernabo JL, Lopez Navarro N, Dominguez G, Zmudzinska M, Herrera Ceballos E. Histological study of basal cell carcinomas recurring after photodynamic therapy: a comparative analysis against its primary tumors. Poster P-20 presented at: 33rd Nordic Congress of Dermatology and Venereology. 27–29 April 2016; Trondheim, Norway.

Boyers LN, Karimkhani C, Naghavi M, Sherwood D, Margolis DJ, Hay RJ, et al. Global mortality from conditions with skin manifestations. J Am Acad Dermatol 2014;71:1137–43.

Cho M, Gordon L, Rembielak A, Woo TC. Utility of radiotherapy for treatment of basal cell carcinoma: a review. Br J Dermatol 2014;171:968–73.

Clark CM, Furniss M, Mackay-Wiggan JM. Basal cell carcinoma: an evidence-based treatment update. Am J Clin Dermatol 2014;15:197–216.

Fremlin GA, Gomez P, Halpern J. Are there sufficient numbers of low-risk basal cell carcinomas to justify general practitioners (family physicians) carrying out basal cell carcinoma surgery? Clin Exper Dermatol 2016;41:138–41.

Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, Margolis DJ, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 2014;134:1527–34.

Hollestein LM, de Vries E, Aarts MJ, Schroten C, Nijsten TE. Burden of disease caused by keratinocyte cancer has increased in The Netherlands since 1989. J Am Acad Dermatol 2014;71:896–903.

Karagas M, Greenberg E. Unresolved issues in the epidemiology of basal cell and squamous cell skin cancer. In: Mukhtar H, editor. Skin cancer: mechanisms and human relevance. Boca Raton, FL: CRC Press; 1995. p. 79–86.

Love EM, Manalo IF, Chen SC, Chen KH, Stoff BK. A video-based educational pilot for basal cell carcinoma (BCC) treatment: a randomized controlled trial. J Am Acad Dermatol 2016;74:477–83.

Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet 2010;375(9715):673–85.

Ozolins M, Williams HC, Armstrong SJ, Bath-Hextall FJ. The SINS trial: a randomised controlled trial of excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma. Trials 2010;11:42.

Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Australas J Dermatol 2015;56:258–67.

Prieto-Granada C, Rodriguez-Waitkus P. Basal cell carcinoma: epidemiology, clinical and histologic features, and basic science overview. Curr Probl Cancer 2015;39:198–205.

Rhodes LE, de Rie MA, Leifsdottir R, Yu RC, Bachmann I, Goulden V, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. Arch Dermatol 2007;143:1131–6.

Roozeboom MH, Aardoom MA, Nelemans PJ, Thissen MR, Kelleners-Smeets NW, Kuijpers DI, et al. Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. J Am Acad Dermatol 2013;69:280–7.

Roozeboom MH, Arits AH, Mosterd K, Sommer A, Essers BA, de Rooij MJ, et al. Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficial basal cell carcinoma: a single-blind, noninferiority, randomized controlled trial. J Invest Dermatol 2016;136:1568–74.

Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and non-randomized trials. Br J Dermatol 2012;167:733–56.

Roozeboom MH, van Kleef L, Arits AH, Mosterd K, Winnepenninckx VJ, van Marion AM, et al. Tumor thickness and adnexal extension of superficial basal cell carcinoma (sBCC) as determinants of treatment failure for methylaminolevulinate (MAL)-photodynamic therapy (PDT), imiquimod, and 5-fluorouracil (FU). J Am Acad Dermatol 2015;73:93–8.

Wang H, Xu Y, Shi J, Gao X, Geng L. Photodynamic therapy in the treatment of basal cell carcinoma: a systematic review and meta-analysis. Photodermatol Photoimmunol Photomed 2015;31:44–53.

Williams HC. Basal-cell carcinoma: no response versus relapse; author's reply. Lancet Oncol 2014;15:e105.

Xiong MY, Korgavkar K, Digiovanna JJ, Weinstock MA. Fluorouracil and other predictors of morpheaform basal cell carcinoma among high-risk patients: the Veterans Affairs Topical Tretinoin Chemoprevention Trial. JAMA Dermatol 2014;150:332–4.