

Treatment of Low-Risk Basal Cell Carcinoma

Citation for published version (APA):

Kelleners-Smeets, N. W. J., Mosterd, K., & Nelemans, P. J. (2017). Treatment of Low-Risk Basal Cell Carcinoma. *Journal of Investigative Dermatology*, 137(3), 539-540. <https://doi.org/10.1016/j.jid.2016.11.021>

Document status and date:

Published: 01/03/2017

DOI:

[10.1016/j.jid.2016.11.021](https://doi.org/10.1016/j.jid.2016.11.021)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Thiele JJ, Schroeter C, Hsieh SN, Podda M, Packer L. The antioxidant network of the stratum corneum. *Curr Probl Dermatol* 2001;29:26–42.

Tosti A. A comparison of the histodynamics of sebaceous glands and epidermis in man: a microanatomic and morphometric study. *J Invest Dermatol* 1974;62:147–52.

Tóth BI, Géczy T, Griger Z, Dózsa A, Seltmann H, Kovács L, et al. Transient receptor potential vanilloid-1 signaling as a regulator of human sebocyte biology. *J Invest Dermatol* 2009;129:329–39.

Wróbel A, Seltmann H, Fimmel S, Müller-Decker K, Tsukada M, Bogdanoff B, et al. Differentiation and apoptosis in human immortalized sebocytes. *J Invest Dermatol* 2003;120:175–81.

Zouboulis CC. Acne and sebaceous gland function. *Clin Dermatol* 2004;22:360–6.

Zouboulis CC, Krieter A, Gollnick H, Mischke D, Orfanos CE. Progressive differentiation of human sebocytes in vitro is characterized by increasing cell size and altering antigen expression and is regulated by culture duration and retinoids. *Exp Dermatol* 1994;3:151–60.

Zouboulis CC, Seltmann H, Abdel-Naser MB, Hossini AM, Menon GK, Kubba R. Effects of extracellular calcium and 1,25 dihydroxyvitamin D3 on sebaceous gland cells in vitro and in vivo [e-pub ahead of print]. *Acta Derm Venereol* 2016; <http://dx.doi.org/10.2340/00015555-2525>.

with treatment success after treatment with imiquimod cream is reported to be 82.5% after a follow-up period of 5 years. However, for some reason, the authors did not use a time-to-event analysis, such as Kaplan Meier analysis, to account for the censored observations in 118 of the 501 originally randomized patients, who were lost to follow-up. Therefore, actual treatment success may be somewhat lower, because the percentage, 82.5%, was based on the 383 patients for whom data on outcome was available after 5 years. Most treatment failures occurred within the first year after treatment. This is in line with the findings of Roozeboom et al. (2016), who recently reported 3-year follow-up data of a randomized clinical trial comparing imiquimod cream with 5-fluorouracil cream and photodynamic therapy. In this study, recurrences after photodynamic therapy continued to occur up to 3 years after treatment. Findings from both trials suggest that imiquimod cream might still represent a clinically useful alternative to SE. The fact that almost no recurrences appeared after the first years of follow-up refutes suggestions of a possible progressive rise in BCC recurrences after 3 years of follow-up and suggestions that recurrences in the imiquimod group were difficult to identify. Furthermore, a concern that recurrences had transformed from superficial to morpoeic forms is rebutted (Williams et al., 2017).

Randomized controlled trials are of great importance in gaining evidence for making a conscious shared decision by physicians and patients.

Currently, no treatment competes with the efficacy of SE for BCC. However, imiquimod cream is probably the best alternative, noninvasive treatment. The trial of Williams et al. (2017) was designed as a noninferiority trial. This means that up-front, a lower efficacy is accepted because the investigators

See related article on pg 614

Treatment of Low-Risk Basal Cell Carcinoma



Nicole W.J. Kelleners-Smeets^{1,2}, Klara Mosterd^{1,2} and Patty J. Nelemans³

With the continuously rising incidence and changing populations of patients with basal cell carcinoma, evidence about the different treatment modalities is mandatory. Randomized clinical trials, such as the surgery versus imiquimod for nodular superficial basal cell carcinoma trial, can provide this evidence. Patients can then be informed about all aspects of alternative treatment options so that conscious, shared decisions can be made.

Journal of Investigative Dermatology (2017) 137, 539–540. doi:10.1016/j.jid.2016.11.021

Basal cell carcinoma (BCC) is the most common skin cancer, and its incidence continues to rise. Surgical excision (SE) is still the most commonly used treatment for BCC, although there are numerous other therapeutic options. Optimal treatment depends on patient and tumor characteristics such as size, location, histological subtype, and previous treatment. A Cochrane review reveals that there is little good quality research on comparative effectiveness of treatments for BCC and that there is a need for head-to-head comparisons of treatments, with long-term follow-up (Bath-Hextall et al., 2007). Trials that

included noninvasive treatments were performed mainly by industry, and they were often placebo controlled. However, it seems more relevant to compare new treatments to the “gold standard,” which is surgery. The Surgery versus Imiquimod for Nodular Superficial basal cell carcinoma (SINS) trial of Williams et al. (2017) is therefore an important study, as it compares a commonly used noninvasive treatment, imiquimod cream, with SE. This randomized clinical trial shows that SE remains the most effective treatment for a primary low-risk superficial or nodular BCC. The percentage of lesions

¹Department of Dermatology, Maastricht University Medical Centre, Maastricht, The Netherlands; ²GROW, School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands; and ³Department of Epidemiology, CAPHRI, School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands

Correspondence: Nicole W.J. Kelleners-Smeets, Department of Dermatology, Maastricht University Medical Centre, P Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: n.kelleners.smeets@mumc.nl

© 2016 The Authors. Published by Elsevier, Inc. on behalf of the Society for Investigative Dermatology.

expected that other aspects of the treatment might compensate for lower efficacy. In the SINS trial, an important assumption, which was based on a prestudy survey among UK dermatologists, was that imiquimod cream needed to have a 90% minimum chance of clinical success to change how BCC is treated. Thus, the current outcome of 82.5% is less than the success percentage considered to be acceptable. Nevertheless, the authors still concluded that imiquimod cream might represent a clinically useful treatment modality, but for different reasons.

Why would dermatologists be willing to accept a treatment for low-risk BCCs that is inferior to SE? At first, incidences continuously rise and the population of patients presenting with a BCC is changing. People now develop their first BCC when in their forties, or even earlier, and they often develop multiple BCCs throughout life. Most patients do not prefer repeated surgeries. Furthermore, we fear that there are not enough dermatologists to treat every low-risk BCC surgically. So, in spite of lower effectiveness, there are certain advantages in using noninvasive treatment. Although SE is relatively quick and efficient, it requires a trained doctor, it can be a traumatic experience for patients, and it may result in a surgical scar. Imiquimod cream has the benefit that patients can treat themselves at home, and there is generally a good cosmetic outcome. Side effects are mostly well tolerated and pain is limited. And, according to the present evidence, 4 of 5 patients with a low-risk BCC will be cured after using imiquimod cream. Recurrence of a low-risk BCC can easily be treated with SE. We therefore agree that not all low-risk BCCs require surgical treatment.

An important aspect to choose for a noninvasive treatment has always been the presumed better cosmetic outcome. But how much better is the cosmetic outcome after noninvasive therapies? Objective evaluation of scars is difficult, and there is no perfect scar assessment method that enables one to compare scars after invasive therapies with the changes that are seen after noninvasive therapies (Mosterd et al., 2013). Second, how important is the cosmetic outcome for the majority of

patients? Interestingly, the cosmetic outcome of imiquimod cream was superior to SE according to ratings by dermatologists, but not according to patients (Bath-Hextall et al., 2014). Acceptance of a surgical scar after cancer treatment seems easier for patients than for dermatologists.

What do patients want? Are they willing to accept treatment with an inferior success rate for low-risk BCC? There is a great variation in patient preferences. From our clinical practice, we know that some patients want to be sure that a BCC is cleared regardless of the inconvenience or scarring associated with surgery. Some patients actually prefer to visit the hospital for a 1- or 2-day photodynamic therapy treatment, whereas other patients prefer to treat themselves at home, in spite of a longer treatment duration. A way to evaluate patient preferences is a discrete choice experiment. The discrete choice experiment technique is an attribute-based approach that quantifies the strength of patients' preferences for the health care services or interventions (Tinelli et al., 2012). In the SINS trial, the discrete choice experiment showed that respondents preferred imiquimod cream to SE, because patients were more worried about cosmetic outcomes and possible side effects than about the chance of clearance and cost of treatment.

Williams et al. (2017) highlight briefly in their discussion paragraph that a possible future strategy to deal with the epidemic of BCC might be to treat low-risk BCCs in the community (by general practitioners) using imiquimod cream and then deal with recurrences surgically. We are doubtful that this is a good idea. From a study performed in the Netherlands, we know that malignant skin tumors were poorly recognized by general practitioners and seborrheic keratoses were often mistaken for nevi (van Rijsingen et al., 2014). A group in the UK added that the prevalence of low-risk BCCs in a general practice is not high enough to maintain competencies in BCC surgery and that dermatologists should continue to provide the lead in skin cancer diagnosis, treatment and management (Fremlin et al., 2016). We agree that, unless there is sufficient training of general practitioners, skin

cancer care is best done by the dermatologist.

In the past, doctors informed their patients about their disease, the treatment options, but in most cases, the doctor chose the treatment. Today, shared decision-making is more common. Patients expect to receive information on all aspects of the disease and the different treatment options, allowing them to make their own decision. Randomized clinical trials such as the SINS trial are of great importance in gaining the evidence that leads to conscious, shared decisions.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

- Bath-Hextall FJ, Perkins W, Bong J, Williams HC. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev* 2007; CD003412.
- Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, Miller PS, et al. Surgery versus Imiquimod for Nodular Superficial basal cell carcinoma (SINS) study group. 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.
- 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 Exp Dermatol* 2016;41:138–41.
- Mosterd K, Arits AHMM, Nelemans PJ, Kelleners-Smeets NWJ. Aesthetic evaluation after non-invasive treatment for superficial basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013;27:647–50.
- 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, non-inferiority, randomized controlled trial. *J Invest Dermatol* 2016;136:1568–74.
- Tinelli M, Ozolins M, Bath-Hextall F, Williams HC. What determines patient preferences for treating low risk basal cell carcinoma when comparing surgery vs imiquimod? A discrete choice experiment survey from the SINS trial. *BMC Dermatol* 2012;12:19.
- van Rijsingen MC, Hanssen SC, Groenewoud JM, van der Wilt GJ, Gerritsen MJ. Referrals by general practitioners for suspicious skin lesions: the urgency of training. *Acta Derm Venereol* 2014;94:138–41.
- Williams HC, Bath-Hextall F, Ozolins M, Armstrong SJ, Colver GB, Perkins W, et al. Surgery versus 5% imiquimod for nodular and superficial basal cell carcinoma: 5-year results of the SINS randomised controlled trial. *J Invest Dermatol* 2017;137:614–9.