

Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma

Citation for published version (APA):

Jansen, M. H. E., Mosterd, K., Arits, A. H. M. M., Roozeboom, M. H., Sommer, A., Essers, B. A. B., van Pelt, H. P. A., Quaedvlieg, P. J. F., Steijlen, P. M., Nelemans, P. J., & Kelleners-Smeets, N. W. J. (2018). Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma. *Journal of Investigative Dermatology*, 138(3), 527-533. <https://doi.org/10.1016/j.jid.2017.09.033>

Document status and date:

Published: 01/03/2018

DOI:

[10.1016/j.jid.2017.09.033](https://doi.org/10.1016/j.jid.2017.09.033)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma

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For the treatment of superficial basal cell carcinoma, a prospective, noninferiority, randomized controlled multicenter trial with 601 patients showed that 5% imiquimod cream was superior and 5-fluorouracil cream not inferior to methyl aminolevulinate photodynamic therapy (MAL-PDT) at 1 and 3 years after treatment. No definite conclusion could be drawn regarding the superiority of imiquimod over 5-fluorouracil. We now present the 5-year follow-up results according to the intention-to-treat analysis. Five years after treatment, the probability of tumor-free survival was 62.7% for methyl aminolevulinate photodynamic therapy (95% confidence interval [CI] = 55.3–69.2), 80.5% for imiquimod (95% CI = 74.0–85.6), and 70.0% for 5-fluorouracil (95% CI = 62.9–76.0). The hazard ratio for treatment failure of imiquimod and 5-fluorouracil were 0.48 (95% CI = 0.32–0.71, $P < 0.001$) and 0.74 (95% CI = 0.53–1.05, $P = 0.09$), respectively, when compared with methyl aminolevulinate photodynamic therapy. Compared with 5-fluorouracil, imiquimod showed a hazard ratio of 0.65 (95% CI 0.43–0.98, $P = 0.04$). In conclusion, 5 years after treatment, the results of this trial show that 5% imiquimod cream is superior to both methyl aminolevulinate photodynamic therapy and 5-fluorouracil cream in terms of efficacy for superficial basal cell carcinoma. We therefore consider 5% imiquimod cream as the first choice for noninvasive treatment in most primary superficial basal cell carcinomas.

Journal of Investigative Dermatology (2018) **138**, 527–533; doi:10.1016/j.jid.2017.09.033

INTRODUCTION

Basal cell carcinoma (BCC), the most common non-melanoma skin cancer among the white population, is an important health problem worldwide and has a rapidly increasing incidence (Flohil et al., 2013; Lomas et al., 2012)

As a result, BCC causes high medical consumption and health care costs (Housman et al., 2003). Although surgical excision is the gold standard for treatment of BCCs, different studies suggest that noninvasive therapies are useful alternatives to surgery for treatment of superficial BCC (sBCC) (Szeimies et al., 2008; Williams et al., 2017). Besides being less invasive, topical therapies also have other advantages like good cosmetic outcome, according to evaluation by physicians (Bath-Hextall et al., 2014; Cosgarea et al., 2013; Szeimies et al., 2008).

Only a few studies on long-term effectiveness of noninvasive treatment of sBCC have been published. Head-to-head studies are pivotal to reach consensus in international BCC guidelines on the first choice noninvasive treatment to compare effectiveness (Roozeboom et al., 2012; Williams et al., 2017). We previously showed that the efficacy of 5% imiquimod cream is superior and 5-fluorouracil cream not inferior to methyl aminolevulinate photodynamic therapy (MAL-PDT) in the treatment of sBCC at 3-year follow-up (Roozeboom et al., 2016). Both creams were also found to be cost effective compared with MAL-PDT 1 year after treatment (Arits et al., 2014). The aim of this study is to report the comparative efficacy of MAL-PDT, imiquimod, and 5-fluorouracil 5 years after treatment.

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; HR, hazard ratio; MAL, methyl aminolevulinate; PDT, photodynamic therapy; sBCC, superficial basal cell carcinoma

Received 27 July 2017; revised 18 September 2017; accepted 20 September 2017; accepted manuscript published online 16 October 2017; corrected proof published online 13 December 2017

RESULTS

Patients

A total of 601 patients with a primary, histologically proven sBCC were randomly assigned to treatment with MAL-PDT ($n = 202$), imiquimod ($n = 198$), or 5-fluorouracil ($n = 201$). Baseline characteristics are presented in Table 1. Additional information on these characteristics can be found in a previous report (Arits et al., 2013). Patient flow from recruitment to the 5-year follow-up visit is shown in Figure 1. All participating patients were invited for a follow-up visit at 5 years after the end of treatment. Five patients (two from the MAL-PDT group and three imiquimod group) who were previously considered lost to follow-up, because they were previously unable or unwilling to attend their follow-up visits, were willing to participate at the 5-year follow-up visit. In five patients, protocol deviations occurred because of strong clinical suspicion of recurrence: surgical excision in three patients and noninvasive treatment in two patients. Because these patients could not be assessed for recurrence during the primary noninvasive treatment during follow-up, they were considered lost to follow-up. A total of 87 patients (14.9%) were lost to follow-up, of whom 32 were treated with MAL-PDT, 31 with imiquimod, and 24 with 5-fluorouracil. Reasons for not completing follow-up were death due to causes unrelated to sBCC or treatment, refusal to attend follow-up visits, and other reasons such as inability of the patient to visit the hospital. The median follow-up period in the study was 64 months (range = 1–93).

Probability of tumor-free survival

From randomization until 5 years after treatment, 70 tumor recurrences were found in the MAL-PDT group, 36 in the imiquimod group, and 57 in the 5-fluorouracil group. Thirteen of the 70 recurrences occurred between 3 and 5 years of follow-up (four after MAL-PDT, two after imiquimod, and seven after 5-fluorouracil treatment) (Figures 1 and 2).

Estimates of the cumulative probability of tumor-free survival, according to the intention-to-treat and per protocol analysis, at 1, 3 and 5 years after treatment are presented in Table 2. At 5 years after treatment, the probability of tumor-free survival is 62.7% for MAL-PDT (95% confidence interval [CI] = 55.3–69.2), 80.5% for imiquimod (95% CI = 74.0–85.6), and 70.0% for 5-fluorouracil

(95% CI = 62.9–76.0). Based on the estimated 5-year tumor-free survival probability of 62.7% for MAL-PDT, the noninferiority margin of 10% for absolute differences in survival probability translates to a noninferiority threshold for the hazard ratio (HR) for treatment failure of 1.37 (log 0.527/log 0.627) (Com-Nougue et al., 1993). Consequently, noninferiority of both creams to MAL-PDT can be concluded if the 95% CIs of the corresponding HRs are entirely below 1.37. Superiority of both creams to MAL-PDT can be concluded if the 95% CIs of the corresponding HRs are entirely below 1.0.

The HR for treatment failure comparing imiquimod with MAL-PDT was 0.48 (95% CI = 0.32–0.71, $P < 0.001$) (Table 3). The data also allow comparison of imiquimod with 5-fluorouracil. The HR of 0.65 (95% CI = 0.43–0.98, $P = 0.04$) shows that imiquimod is also superior to 5-fluorouracil. Comparison of 5-fluorouracil with MAL-PDT resulted in an HR of 0.74 (95% CI = 0.53–1.05, $P = 0.09$). According to the intention-to-treat analysis, after 5 years of follow-up, imiquimod was superior compared with MAL-PDT and 5-fluorouracil. 5-fluorouracil is not inferior to MAL-PDT. Almost identical results were found in the per protocol analysis (Tables 2 and 3). A sensitivity analysis, wherein the tumors of the five patients with protocol deviations were considered as recurrences instead of lost-to-follow-up, indicated robustness of the results (see Supplementary Tables S1 and S2 online).

Based on the 5-year probabilities of remaining free from recurrence, one recurrence can be prevented for every 5.6 patients (95% CI = 3.7–11.4) treated with imiquimod instead of MAL-PDT and for every 9.5 patients (95% CI = 5.2–57.4) treated with imiquimod instead of 5-fluorouracil.

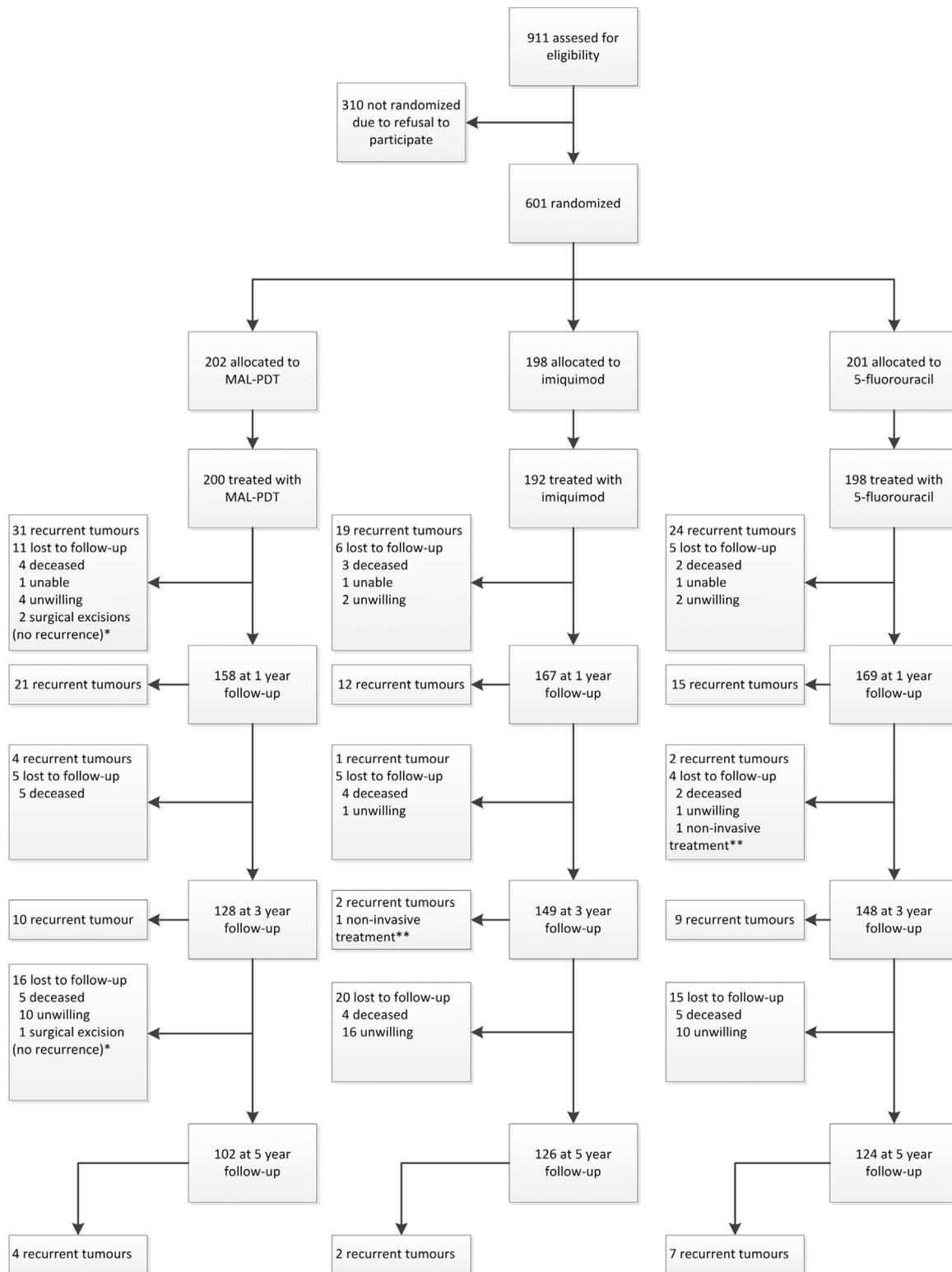
DISCUSSION

The results of our study showed that treatment with 5% imiquimod cream is superior to both MAL-PDT and 5-fluorouracil in treatment of sBCC, 5 years after treatment, in terms of efficacy. To our knowledge, this is the first prospective head-to-head comparison study on three different noninvasive therapies in the treatment of sBCC with a follow-up of 5 years. We confirmed superiority of 5% imiquimod cream over MAL-PDT and also found evidence for superiority of imiquimod over 5-fluorouracil cream, which had not yet

Table 1. Distribution of patient and tumor characteristics

Characteristic	MAL-PDT (n = 202)	Imiquimod cream (n = 198)	5-fluorouracil cream (n = 201)
Sex, n (%)			
Male	96 (48)	102 (52)	106 (53)
Female	106 (52)	96 (48)	95 (47)
Median age in years (range)	63 (26–87)	62 (30–91)	64 (35–86)
Median tumor size in mm ² (range)	52 (5–1,382)	63 (5–1,413)	63 (9–5,472)
Tumor location, n (%)			
Head/neck (reference)	24 (12)	23 (12)	31 (15)
Trunk	119 (59)	121 (61)	120 (60)
Upper extremities	32 (16)	26 (13)	27 (13)
Lower extremities	27 (13)	28 (14)	23 (11)

Abbreviations: MAL-PDT, methyl aminolevulinate photodynamic therapy.



*Surgical excision was done in three patients due to a strong clinical suspicion of recurrence. Since these patients could not be assessed for recurrence during follow-up, they were considered lost to follow-up. ** Non-invasive treatments were given in two patients due to a strong clinical suspicion of recurrence. Since these patients could not be assessed for recurrence to the primary non-invasive treatment during follow-up, they were considered lost to follow-up.

Figure 1. CONSORT flow chart, patient flow.

Figure 2. Kaplan-Meier Survival plot.

MAL-PDT, methylaminolevulinate photodynamic therapy.

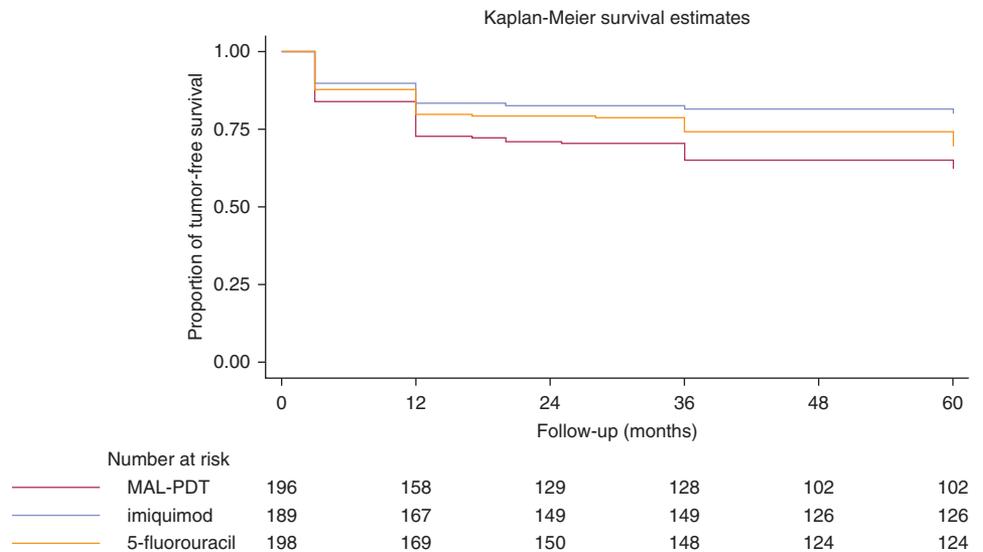


Table 2. Cumulative probability of tumor-free survival 1, 3, and 5 years after treatment with MAL-PDT, imiquimod, or 5-fluorouracil for sBCC

Time after Treatment	MAL-PDT		Imiquimod		5-Fluorouracil	
	ITT, % (95% CI)	PP, % (95% CI)	ITT, % (95% CI)	PP, % (95% CI)	ITT, % (95% CI)	PP, % (95% CI)
1 year	73.0 (66.1–78.7)	73.4 (66.6–79.0)	83.5 (77.4–88.1)	83.5 (77.4–88.1)	80.1 (73.8–85.0)	79.8 (73.4–84.8)
3 year	65.3 (58.0–71.6)	65.3 (58.1–71.5)	81.8 (75.5–86.7)	81.8 (75.5–86.7)	74.2 (67.4–79.8)	74.4 (67.5–80.0)
5 year	62.7 (55.3–69.2)	62.7 (55.4–69.2)	80.5 (74.0–85.6)	80.5 (74.0–85.6)	70.0 (62.9–76.0)	70.1 (62.9–76.1)

Abbreviations: CI, confidence interval; ITT, intention to treat; MAL-PDT, methyl aminolevulinat photodynamic therapy; PP, per protocol; sBCC, superficial basal call carcinoma.

Table 3. Absolute differences and HRs with 95% CI of tumor-free survival at 5-year follow-up

	Intention-to-Treat Analysis			Per Protocol Analysis		
	Difference, %	HR (95% CI)	P	Difference, %	HR (95% CI)	P
Imiquimod versus MAL-PDT	17.8	0.48 (0.32–0.71)	<0.001	17.8	0.48 (0.33–0.72)	<0.001
5-fluorouracil versus MAL-PDT	7.3	0.74 (0.53–1.05)	0.09	7.4	0.74 (0.53–1.05)	0.09
Imiquimod versus 5-fluorouracil	10.5	0.65 (0.43–0.98)	0.04	10.4	0.65 (0.43–0.98)	0.04

Abbreviations: CI, confidence interval; HR, hazard ratio; MAL-PDT, methylaminolevulinat photodynamic therapy.

manifested itself at 1 and 3 years of follow-up (Arits et al., 2013; Roozeboom et al., 2016).

Our finding that imiquimod has a tumor-free survival of 80.5% after 5 years of follow-up is comparable with findings of other studies. A recent randomized controlled trial by Williams et al. (2017), which compared surgical excision with topical imiquimod cream in 501 patients with sBCC, reported a 5-year success rate of 83.8%. Only one recurrence was found between 3 and 5 years of follow-up after treatment with imiquimod, which is comparable to the low number of recurrences (n = 2) found in our study in the same follow-up interval. Two other studies on imiquimod treatment for sBCC reported 5-year success rates of 80.4% (95% CI = 74.4–86.4%) and 77.9% (Gollnick et al., 2008; Quirk et al., 2010).

The results of this study showed that MAL-PDT has a probability of tumor-free survival of 62.7% at 5 years after treatment. Only one other study on MAL-PDT with a 5-year follow-up period is available for comparison (Basset-Seguín et al., 2008). This study included 114 sBCCs in 60 patients and showed a 5-year success rate of 75% (95% CI = 64.3–83.3%). This discrepancy may be explained by the fact that the latter study retreated patients with initial incomplete response and excluded patients that had a treatment failure at 3 months. This introduces bias toward a more favorable long-term result of PDT. To the best of our knowledge, no studies with long-term follow-up results after treatment with 5-fluorouracil for sBCC have been published. The efficacy of 5-fluorouracil in the treatment of sBCC was evaluated in one study (Gross et al., 2007). This study used a

longer treatment regimen of 6 to 12 weeks and reported a cure rate of 90% at 3 weeks after treatment. A longer treatment period might positively influence the results of 5-fluorouracil.

In the European Guidelines, updated in 2014, all three studied noninvasive therapies are considered as an effective treatment for sBCC (Trakatelli et al., 2014). Our data suggest that based on efficacy, 5% imiquimod cream should be the noninvasive treatment of first choice. PDT and 5-fluorouracil could be reserved for situations where there is a relative or absolute contraindication to using imiquimod. PDT may be more effective in specific subgroups of patients. We previously performed subgroup analyses indicating that in older patients with an sBCC on the lower extremities, MAL-PDT was significantly more effective than imiquimod. (Roozeboom et al., 2015, 2016) Because our study was not designed for subgroup analyses, these findings need to be validated in another study.

Patient preferences should also be considered when choosing a therapy. A discrete choice experiment, which was performed alongside our study, showed that effectiveness of a therapy was the most important driver for treatment preference (Essers et al., 2017). A study by Martin et al. (2016) also showed that 124 patients with a BCC valued a high chance of cure the most, but when the BCC was located in the head or neck region and if the BCC was recurrent, patients were willing to trade risk of recurrence for better cosmetic results. Two other discrete choice experiments showed that patients preferred a better cosmetic result rather than a higher level of effectiveness. It must be noted that in these studies topical treatments (MAL-PDT or imiquimod cream) were compared with surgical excision (Tinelli et al., 2012; Weston, 2004). Furthermore, adverse events should also be taken into account. As previously reported, all therapies showed local adverse events, such as pain or skin redness (Arits et al., 2013). Patients treated with creams more often reported moderate to severe local swelling, erosion, crust formation, and itching of the skin than patients treated with MAL-PDT. However, for all studied treatments, no major adverse events were reported (Arits et al., 2013). From a cost perspective, 5-fluorouracil may be considered an attractive alternative, because costs of 5-fluorouracil are much lower than costs of imiquimod. In The Netherlands, the cost of a 40-g tube of 5-fluorouracil is €31.32, compared with €177.41 for 36 sachets of imiquimod 5% cream (Medicijnkosten, 2017) However, because of the much higher risk of recurrences 5 years after treatment with 5-fluorouracil, we do not think that, from a clinical perspective, the potential higher cost savings can justify the lower efficacy. When choosing a treatment, the various treatment aspects should be taken into account to enable patients with an sBCC to make a well-informed decision.

A limitation of this study is the loss-to-follow-up of 87 out of 601 randomized patients (14.9%), which is a common problem in studies with long-term follow-up. For logistic reasons it was not possible to plan all control visits at exactly 1, 3, and 5 years after the end of treatment. Actual dates of follow-up visits could take place before or after the pre-planned dates. For this reason, the previously published 3-year results show some discrepancies with the 3-year

results reported in this study (Roozeboom et al., 2016). In this study, patient observations were censored at exactly 36 months after treatment (the planned date), whereas in the previous report, the actual date of the 3-year follow-up visit was used for censoring when this date preceded the planned date. The absolute 3-year probabilities of tumor-free survival for all three noninvasive treatments were therefore slightly underestimated compared with the absolute probability estimates in this article. However, the estimates of the relative effectiveness of the three treatment modalities were not affected.

In conclusion, the results of this trial show that after 5 years of follow-up, 5% imiquimod is superior to both MAL-PDT and 5-fluorouracil in treatment of patients with primary sBCC. We therefore consider 5% imiquimod as the first choice noninvasive treatment in most primary sBCCs in terms of efficacy. However, there is a need for multiple experiments from disparate investigators showing a similar trend/outcome.

MATERIALS AND METHODS

Protocol

Long-term results were evaluated with data from a single-blinded, noninferiority, multicenter study in which patients with sBCC were randomized between treatment with MAL-PDT, imiquimod, or 5-fluorouracil cream (Arits et al., 2013). Patients were recruited at the dermatology departments of seven hospitals in The Netherlands between March 2008 and August 2010. The extensive study design and procedures have been described elsewhere, but will be briefly described here (Arits et al., 2013; Roozeboom et al., 2016).

Primary inclusion criteria for the 601 participants were patients with a primary sBCC that was histologically confirmed on a 3-mm punch skin biopsy. One tumor per patient was included. Excluded were patients using immunosuppressive drugs, suffering from genetic cutaneous cancer disorders, having tumors located in the high-risk area of the face (H-zone) or scalp, and women who were pregnant or breastfeeding.

Treatment with MAL-PDT (Metvix, Galderma SA, Penn Pharmaceutical Services, Gwent, UK) involved two single treatments with a 1-week interval (fluence = 630 nm, dose = 37 J/cm²). Patients randomized to receive 5% imiquimod cream (Aldara, Meda AB, Solna, Sweden) applied the cream once daily for 5 consecutive days a week for 6 weeks. Treatment with 5% 5-fluorouracil cream (Efudix, Meda Pharmaceuticals, Amstelveen, Netherlands) involved application of the cream twice daily for 4 weeks.

The primary study outcome in this study was defined as the cumulative probability of remaining free of tumor recurrence at 5 years after treatment, which is referred to as the 5-year probability of tumor-free survival. Treatment failure was defined as a histologically confirmed BCC on a skin biopsy sample from a clinically suspect area within 10 mm of the scar of the biopsy. Follow-up visits were planned at 3, 12, 36, and 60 months after end of treatment and were performed by an investigator who was blinded to treatment assignment.

The study was performed in accordance with the Declaration of Helsinki Principles, and approval of the local medical ethics and scientific committee of the Maastricht University Medical Centre was obtained. All participants provided written, informed consent before enrolment. The trial was registered as International Standard Randomized Controlled Trial (ISRCTN 79701845).

Assignment and masking

Participants were randomly assigned to one of the three treatments in a 1:1:1 ratio. Stratifying factors were age and tumor location (head/neck vs. other). Follow-up visits were performed by an investigator who was blinded to treatment assignment and was not involved in the treatment. Patients and treating physicians were not blinded to the allocated treatment.

Participant flow and follow-up

All participating patients were invited for a follow-up visit at 5 years after the end of treatment. For logistical reasons, follow-up visits were planned within a window of 6 months before or 6 months after the actual 5-year follow-up date.

Statistical analysis

Effectiveness. For descriptive purposes, categorical variables were presented as numbers and percentages, and mean (\pm standard deviation) or median with range were reported for continuous variables. The original sample size of 197 patients per randomized group was based on the statistical ability to detect an absolute difference of 10% in 1-year probability of tumor-free survival (non-inferiority margin) between groups, with a power of 80% and one-sided alpha of 5%. The full rationale for the sample size calculation of this study has been described in earlier publications on this trial (Arits et al., 2013; Roozeboom et al., 2016).

Time-to-event analyses were performed to account for differences in follow-up between patients. In case of recurrence of a treated lesion, patients were censored at the date of recurrence or at the date of last follow-up visit. Because of logistic reasons, the actual date of follow-up visits did not always coincide exactly with the planned dates (at 3, 12, 36, and 60 months after treatment). For the Kaplan-Meier analysis, we used the planned dates, assuming that the observed health state (treatment failure or not) reflected the health state at the moment that the visit should have taken place.

Cox proportional hazards models were used to calculate hazard ratios for treatment failure with 95% CIs. To facilitate interpretation of HRs, the noninferiority margin of 10% for absolute differences in tumor-free survival probability was translated into a noninferiority threshold on the relative risk scale based on the observed 5-year tumor-free survival probability (p_0) in the MAL-PDT group ($\log[p_0 - 0.1]/\log[p_0]$) (Com-Nougue et al., 1993). Both intention-to-treat and per protocol analyses were performed.

All data were analyzed using SPSS, version 23.0 (IBM, Armonk, NY) and STATA, version 14.0 (STATA, College Station, TX).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We thank the patients who agreed to participate in this study. We thank M. de Rooij, C. Thissen, J. Rijzewijk, and A. van Geest for contributing to this study. We thank all nurse practitioners, nursing staff, and employees of the secretarial department of the participating hospitals. We thank Nicole Luckerhof for her excellent administrative support. We thank Kiki Frencken for her unrelenting commitment to and enthusiasm for this study.

The study was financed by a grant of The Netherlands Organization for Scientific Research (ZonMw) (08-82310-98-08626). ZonMw is a governmental institution financing research to improve health care in The Netherlands. The funding source had no role in the design or conduct of the study collection; management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

The trial is registered as an International Standard Randomized controlled trial (ISRCTN) 79701845. Date of clinical trial registration: 30 April 2008.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at <https://doi.org/10.1016/j.jid.2017.09.033>.

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