
Surgery versus combined treatment with curettage and imiquimod for nodular basal cell carcinoma: One-year results of a noninferiority, randomized, controlled trial



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Purpose: Nodular basal cell carcinoma (nBCC) is mostly treated with surgical excision. Interest in minimally invasive treatment of these low-risk tumors is increasing. We assessed the effectiveness of nBCC treatment with curettage and imiquimod cream compared with surgical excision.

Methods: Patients with nBCC included in this randomized, controlled noninferiority trial were randomly assigned to either a curettage and imiquimod cream group or a surgical excision group. The primary endpoint was the proportion of patients free from treatment failure 1 year after the end of treatment. A prespecified noninferiority margin of 8% was used. A modified intention-to-treat and a per-protocol analysis was performed ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02242929) identifier NCT02242929).

Results: One hundred forty-five patients were randomized: 73 to the curettage and imiquimod cream group and 72 to the surgical excision group. The proportion of patients free of recurrence after 12 months was 86.3% (63/73) for the curettage and imiquimod group and 100% (72/72) for the surgical excision group. The difference in efficacy was -13.7% (95% confidence interval -21.6% to -5.8%; 1-sided $P = .0004$) favoring surgical excision.

Conclusion: Noninferiority of curettage and imiquimod cream cannot be concluded. Given the still high efficacy of curettage and imiquimod cream and the indolent growth pattern of nBCC, curettage and imiquimod could still be a valuable treatment option with the possibility to prevent overuse of excisions. However, it cannot replace surgical excision. (*J Am Acad Dermatol* 2020;83:469-76.)

Key words: basal cell carcinoma; imiquimod cream; nonmelanoma skin cancer; skin cancer; surgical excision; therapy; treatment.

Basal cell carcinoma (BCC) is a slowly growing, locally invasive skin tumor and the most common malignant disease in white patients.¹ A simplified histologic classification of

BCCs distinguishes between nodular, superficial, and infiltrative variants, with nodular BCC (nBCC) being the most frequent subtype.² Standard treatment of nBCC is surgical excision (SE). Because of

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the increasing incidence of BCC, its treatment puts a high burden on dermatologic practice. Superficial and nBCCs in low-risk areas are generally accepted to be low-risk tumors with a slow growth pattern and low invasive potential, which has encouraged research on the effectiveness of noninvasive and minimally invasive treatment options. Surgical excision may be accompanied by complications (postoperative bleeding, secondary infection, and disfiguring scars), which is even more relevant in patients who develop multiple BCCs.³ Noninvasive treatments, such as imiquimod cream, 5-fluorouracil, or photodynamic therapy are currently registered and commonly used for treatment of superficial BCC. Of those, imiquimod proved to be superior with clearance rates of 80.5% at 5 years after treatment.^{1,4}

Imiquimod cream treatment for nBCC has been investigated in a randomized, controlled, double blind, dose response trial with a surgical excisional endpoint by Shumack et al,⁵ and optimal cure rates were found for once daily dosing for 7 days per week. Clearance was evaluated after treatment and cure rates were 71% and 76% after 6- and 12-week daily treatment regimens, respectively.⁵ Recently, Williams et al⁶ compared the effectiveness of a 12-week imiquimod cream treatment regimen to surgical excision of low-risk superficial BCC and nBCC after 3 and 5 years of follow-up. Imiquimod already showed a high efficacy of 82.5% after 5 years of follow-up but was still inferior to surgery.⁶

A treatment strategy mentioned in guidelines for low-risk nBCC is curettage and electrodesiccation, but it often leads to a poor cosmetic result with hypertrophic scarring, probably because of the destruction after electrodesiccation.^{1,7,8} Curettage alone is not deemed an accepted treatment modality for nBCC.⁹ We hypothesized that combining the mechanic effect of curettage with the immunologic antitumor effect of imiquimod cream could enable a deeper penetration of imiquimod into the tumor. Combining curettage with imiquimod cream for nBCC was already investigated in some small phase II and III pilot studies, showing efficacy rates (initial and sustained tumor clearance) ranging from 94% to 100% with follow-up of 6 weeks to 1 year.¹⁰⁻¹²

We aimed to evaluate whether curettage followed by imiquimod cream 5% is noninferior to surgical

excision in the treatment of patients with low-risk nBCC.

METHODS

A multicenter, randomized, controlled noninferiority trial was performed at the outpatient clinics of the Maastricht University Medical Centre, Maastricht, and Catharina Hospital, Eindhoven. Eligible patients had a primary nBCC of 4 mm to 20 mm, histologically proven by a specialized dermatopathologist from a 3-mm biopsy specimen.¹³ Mixed type BCCs having a superficial and nodular component were also included.

One lesion per patient was included to ensure independence of observations. When patients had >1 BCC, the most accessible lesion or

the largest lesion was chosen. Exclusion criteria were: localization in the H-zone of the face or on the hairy scalp, recurrent BCC and BCC with (partly) an aggressive histopathologic subtype (infiltrative, BCC with squamous differentiation), patient life expectancy of <5 years, breastfeeding or pregnancy, serious comorbidities (overall health status/diseases of the patient that makes follow-up impossible), genetic skin cancer syndromes, or the use of immunosuppressive medication during the trial period until 3 months after the end of treatment or within 30 days before enrollment. This trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the local independent ethics committee and all patients provided written informed consent.

The primary study endpoint was the proportion of patients free from treatment failure 1 year after the end of treatment, defined as the absence of residual tumor after 3 months or of local recurrence after 1 year posttreatment.

Patients treated with imiquimod cream had a follow-up visit scheduled at 3 months and both treatment groups had a visit at 12 months after treatment. Two investigators independently examined patients for clinical signs (shiny border, telangiectasia, and ulceration) and dermoscopic characteristics (telangiectasia or ovoid nests) of residual or recurrent tumor as is usually done in standard care. In the event that one of the investigators suspected initial treatment failure or recurrence, a 3-mm punch biopsy specimen was obtained for histologic verification. Only in cases of histologic

CAPSULE SUMMARY

- Nodular basal cell carcinoma is a common and indolent skin cancer and surgical excision is the standard treatment.
- Curettage and imiquimod is a minimally invasive treatment alternative that decreases the workload on dermatologic practice and enables treatment for patients at home.

confirmation of BCC was the lesion considered as a treatment failure.

Secondary endpoints were compliance, cosmetic outcomes, patient satisfaction, and pain and adverse events 1 year posttreatment. Cosmetic outcome was assessed independently by 2 investigators and the patients on respectively a 4-point scale (poor, fair, good, or excellent) and patient and observer scar assessment scale.¹⁴

Patients were asked for adverse reactions during follow-up visits, completed diaries to report daily on compliance and pain (on a 10-point visual analogue scale where 0 represents “no pain” and 10 represents the “most severe pain imaginable”) during treatment and 2 weeks after treatment. Patient satisfaction was evaluated by asking 3 standard questions.

Procedures

Patients allocated to surgical excision could undergo this procedure on the day of randomization. The nBCC was excised under local anesthesia (lidocaine 1%) with a 3-mm clinically tumor-free safety margin into the subcutaneous fat.¹⁵

Sutures were removed 1 to 2 weeks postoperatively, depending on tumor localization. Histologic examination was performed by pathologists on tumor margins using postoperative hematoxylin–eosin-stained vertical sections taken from formalin-fixed, paraffin-embedded tissue.

Patients assigned to the curettage and imiquimod 5% cream group underwent curettage only of the elevated tumor tissue, up to the level of normal skin at the day of randomization. To allow healing of the erosion, imiquimod 5% cream was started 1 week after curettage. The dosing regimen was a 6-week application, 5 days a week, once a day. Patients were instructed to apply the cream in a thin layer on the tumor including 5 mm to 10 mm of the surrounding skin, to use no occlusive dressing, and to apply the cream at least 1 hour before going to bed and to wash it off the next morning.

All suspected unexpected serious adverse reactions were recorded in the national registry (toetsingonline.com).

Randomization and masking

Patients were randomly assigned to either topical imiquimod 5% cream and curettage or surgical excision groups using a computer-generated randomization list with random permuted blocks of 4. Randomization was stratified for participating center. Blinding of patients and physicians to treatment assignment was not feasible because of different scarring.

Statistical analysis

The prespecified noninferiority margin was set at 8% (assuming an efficacy of 98% after surgical excision and considering that curettage with imiquimod 5% cream is inferior if the efficacy would fall below 90%). A sample size of 130 patients (65 per group) was required to be 90% sure that the lower limit of a 2-sided 95% (1-sided 97.5%) confidence interval would exclude a difference in favor of the standard group of >8%. To account for a loss to follow-up of 10%, 144 patients were needed.

The absolute difference in the proportion of participants without treatment failure between randomized groups at 1 year posttreatment was calculated with a 2-sided 95% confidence interval (95% CI). Negative differences indicate lower success rates for curettage with imiquimod 5% cream compared with excision. Both an intention to treat and a per protocol analysis were performed.

Differences in secondary endpoints were calculated with the chi-square test and *t* test for independent samples.

All data were analyzed with SPSS software (v 23.0; IBM Corp, Chicago, IL). This study is registered on clinicaltrials.gov (NCT02242929).

RESULTS

Between January 2016 and November 2017, 310 patients were assessed for eligibility (Fig 1). Of those, 165 declined to participate because of a strong preference for 1 of the 2 treatments, difficulties to apply cream because of lesion location, older age, or comorbidities. The BCC size of patients declining participation were comparable to those of the included participants. One hundred forty-five patients were included and randomly assigned to treatment with either curettage and imiquimod cream (n = 73) or surgical excision (n = 72) in 2 hospitals: Maastricht University Medical Centre (n = 137) and Catharina Hospital Eindhoven (n = 8). All patients received the allocated treatment. Four patients (2.8%) were lost to follow-up (Fig 1).

Baseline characteristics are shown in Table I. There were slight imbalances between the treatment groups, with higher frequencies of female sex, Fitzpatrick skin type 1, and location of the lesion in head and neck region in the patients assigned to the curettage and imiquimod group. Positive history of BCC was less often reported in this group.

Primary endpoint

One year after treatment, the proportion of patients free from treatment failure was 86.3% (63/73) for the curettage and imiquimod cream group and 100% (72/72) for the surgical excision group.

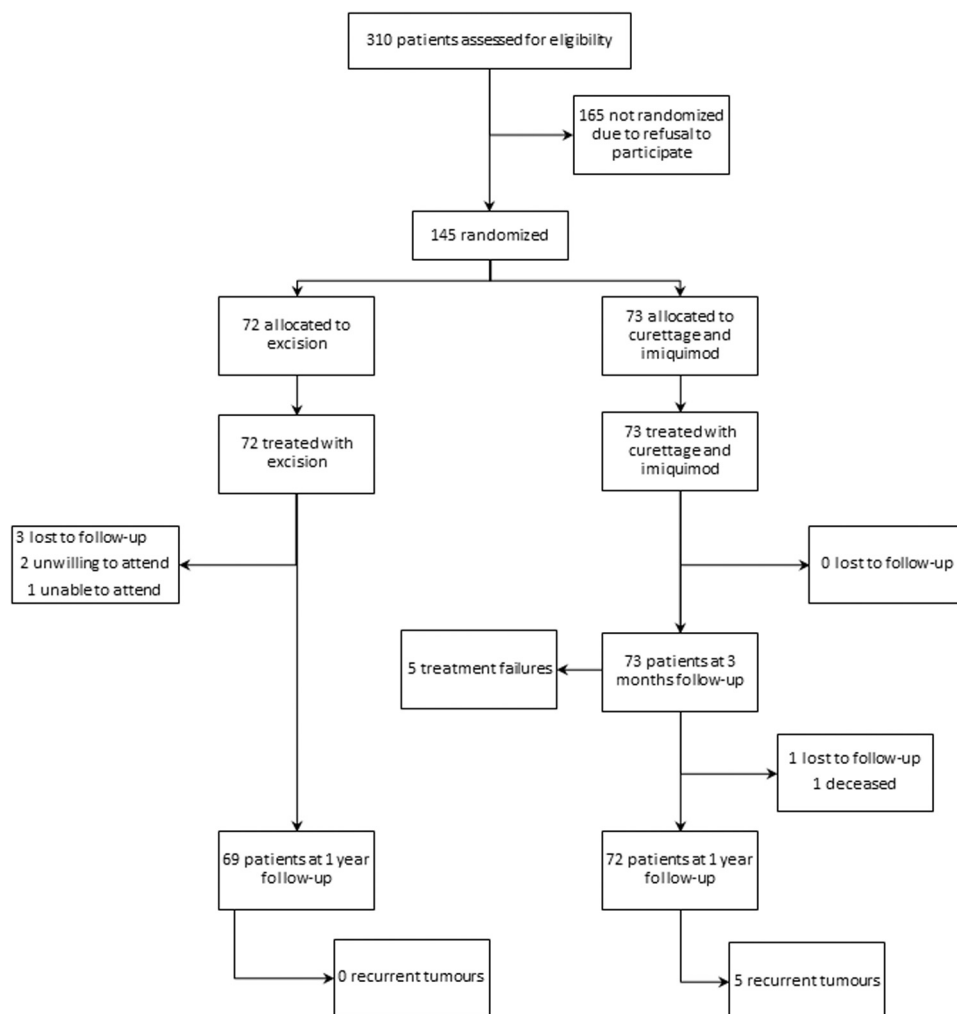


Fig 1. Study flowchart.

The absolute difference was -13.7% (95% CI -21.6% to -5.8% ; 1-sided $P = .0004$) favoring surgery. The lower limit of the 95% CI exceeds the noninferiority margin of -8% and so it cannot be concluded that curettage with imiquimod is noninferior to surgical excision (Fig 2).

Per-protocol analyses resulted in similar results with an absolute difference of -12.5% (95% CI -20.1% to -4.7% ; 1-sided $P = .0009$). Residual or recurrent tumors in the curettage and imiquimod group were found on the trunk ($n = 4$), head/neck ($n = 4$), and lower extremities ($n = 2$). Histopathology showed 1 superficial, 7 nodular, and 2 aggressive BCCs (1 infiltrating, 1 basosquamous).

Subgroup analyses

The median value of BCC size (7 mm) was used as the cutoff for subgroup analyses of the nBCC size. For patients with BCCs ≤ 7 mm, the absolute difference was -14.7% (95% CI -26.6% to -2.8% ; 1-sided

$P = .008$), and for patients with BCCs > 7 mm the difference was -12.8% (95% CI -23.3% to -2.3% ; 1-sided $P = .03$), both in favor of surgical excision.

Secondary endpoints

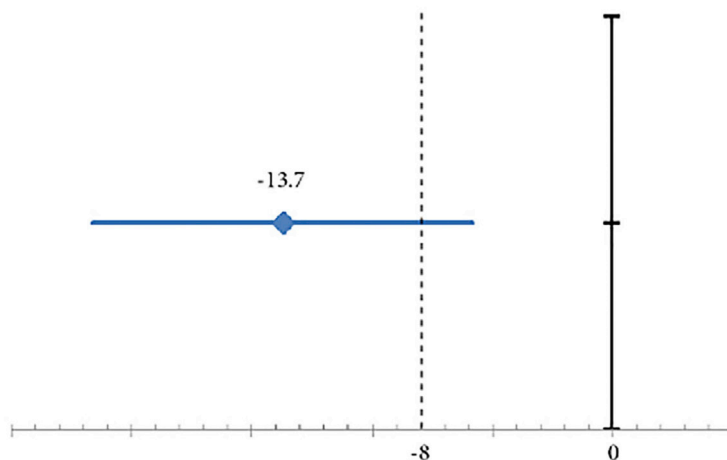
The proportions of patients with residual tumor at 3 months after treatment were 6.8% (5/73) in the curettage and imiquimod group and 0% (0/72) in the surgical excision group (1-sided $P = .030$).

Pain scores revealed that patients treated with curettage and imiquimod cream less often reported moderate to severe pain (13.5%) compared with patients in the excision group (27%), but the differences were nonsignificant ($P = .208$; Table II). The proportions of patients receiving curettage and imiquimod that reported moderate to severe adverse events varied from 1.7% (for squamiae) to 30% (for redness) (Table II). Patients did not report flu-like

Table I. Distribution of patient and tumor characteristics

Characteristics	Total (N = 145)	Curettage and imiquimod (n = 73)	Excision (n = 72)
Sex, n (%)			
Male	77 (53.1)	33 (45.2)	44 (61.1)
Female	68 (46.9)	40 (54.8)	28 (38.9)
Median age, y (range)	68 (31-89)	68 (38-89)	67 (31-87)
Fitzpatrick skin type, n (%)			
I	55 (37.9)	35 (47.9)	20 (27.8)
II	90 (62.1)	38 (52.1)	52 (72.2)
History of BCC, n (%)			
Yes	89 (61.4)	38 (52.1)	51 (70.8)
No	56 (38.6)	35 (47.9)	21 (29.2)
Sun exposure, n (%)			
Mild	1 (0.7)	0 (0)	1 (1.4)
Moderate	121 (83.4)	58 (79.5)	63 (87.5)
Severe	23 (15.9)	15 (20.5)	8 (11.1)
Size BCC, n (%)			
Median, mm (range)	7 (4-20)	8 (4-20)	7 (4-20)
≤7 mm	75 (52.8)	34 (46.6)	41 (59.4)
>7 mm	67 (47.2)	39 (53.4)	28 (40.6)
Location, n (%)			
Head/neck	43 (29.7)	25 (34.2)	18 (25)
Trunk	56 (38.6)	25 (34.2)	31 (43.1)
Upper extremities	23 (15.9)	12 (16.4)	11 (15.3)
Lower extremities	23 (15.9)	11 (15.1)	12 (16.7)
Study site, n (%)			
Maastricht	137 (94.5)	69 (94.5)	68 (94.5)
Eindhoven	8 (5.5)	4 (5.5)	4 (5.5)

BCC, Basal cell carcinoma.



	Difference(%)	95% CI*	P-value
Curettage&imiquimod vs. surgical excision	-13.7%	-21.6% to -5.8%	0.0004

*95% confidence interval

Fig 2. Absolute difference in efficacy between curettage and imiquimod versus surgical excision. The figure shows the absolute difference in treatment efficacy 1 year after treatment (−13.7%) and the horizontal line represents the 95% confidence interval (−21.6% to −5.8%). The lower boundary of the 95% confidence interval crosses the noninferiority limit of −8%.

Table II. Pain and adverse events during and 2 weeks after treatment reported by patients*

	Curettage and imiquimod	Surgery
Pain score (VAS), n (%)		
Absent/mild	51/59 (86.4)	38/52 (73)
Moderate	6/59 (10.2)	11/52 (21)
Severe	2/59 (3.4)	3/52 (6)
Curettage and imiquimod treatment adverse events, n (%)	Absent/mild	Moderate/severe
Redness	42 (70)	18 (30)
Erosion	45 (75)	15 (25)
Crusts	45 (75)	15 (25)
Squamae	59 (98.3)	1 (1.7)
Itching	57 (95)	3 (5)

VAS, Visual analogue scale.

*Pain and adverse events were recorded in diaries, so data were missing for some participants. Pain scores are categorized into 3 groups: absent/mild, 0-3; moderate, 4-6; and severe, 7-10. Adverse events are categorized into 2 groups: absent/mild and moderate/severe.

symptoms in their diaries. No suspected unexpected serious adverse events occurred in this study.

Data on cosmetic outcomes are shown in [Table III](#). Investigator-reported cosmetic outcome after curettage and imiquimod was significantly better than after surgical excision, but patient ratings of cosmetic results were similar in both treatment groups ([Table III](#)). An exception concerned the subgroup of BCCs located in the head and neck, where the patient reported that cosmetic outcome was significantly better after curettage and imiquimod than after surgical excision ($P = .02$).

Patient satisfaction results are shown in [Table IV](#).

Compliance was 100% in the excision group. Complete compliance was reported in 76.3% (45/59) of patients in the curettage and imiquimod group.

DISCUSSION

Surgical excision was significantly more effective than curettage and imiquimod in this study. With a difference of -13.7% and the lower limit of the CI falling below the prespecified noninferiority margin of -8% , it cannot be concluded that curettage followed by imiquimod cream is noninferior to surgical excision. This conclusion also holds for smaller nBCCs (≤ 7 mm).

The probability of being free from treatment failure at 1 year after the end of treatment was 86.3% and comparable to the 1-year success rate of 85.6% that was found in the excisional surgery versus

imiquimod 5% cream for nodular and superficial basal cell carcinoma (SINS) trial for the subgroup with nBCC. No curettage was performed in the SINS trial, but imiquimod treatment was applied for 12 weeks instead of 6 weeks.

Previous phase II to III pilot studies already found higher efficacy rates of 94% to 100% after curettage and imiquimod in the treatment of nBCC. However, these studies had shorter follow-up, used study populations that also included patients with superficial BCC, or applied imiquimod during a longer period (≤ 12 weeks of treatment).¹⁰⁻¹²

The similar success rates after imiquimod treatment of nBCC in this trial and the SINS trial raise the question whether the addition of curettage increases the effectiveness of imiquimod treatment. Curettage may allow for a shorter imiquimod application period of 6 weeks instead of 12 weeks, but this needs to be investigated.

This trial does not allow the conclusion that imiquimod treatment with curettage is noninferior to surgical excision. Nevertheless, the success rates of curettage and imiquimod still represent a substantial response.

In international guidelines, noninvasive treatment is already generally accepted as standard care for superficial BCC. There seems to be no obvious reason to follow another approach for nBCC than for superficial BCC, because both subtypes are considered low risk and in the SINS trial 3-year clearance rates for nBCC were not much lower than for sBCC (81.8% and 85.1%, respectively). The high incidence of BCC puts a burden on the workload of dermatologists, and therefore curettage and imiquimod can be a valuable treatment alternative. Especially in patients with multiple lesions, this treatment increases capacity and might be cost effective.

We found that clinical observers rated the cosmetic outcomes after curettage and imiquimod 5% cream significantly better than after surgery. Patients reported that the cosmetic outcomes of curettage and imiquimod were significantly better for nBCC localized in the head and neck region compared with excision. The visibility of this region and the possible avoidance of reconstructive surgery can be causes for this finding.

There were no flu-like symptoms reported. This is possibly because imiquimod cream was only applied to 1 small, solitary lesion.

A limitation of our study is that a total of 53.2% of the patients eligible for this study did not want to participate. Although it seems unlikely that this selection bias affects the estimate of efficacy, this problem, common to randomized controlled trials,

Table III. Cosmetic outcomes

	Curettage and imiquimod	Surgery	P value (2-tailed)
Four-point scale, n (%)	Good/excellent	Good/excellent	
Observer 1	61/71 (85.5)	47/69 (68.1)	.012
Observer 2	59/71 (83.1)	31/68 (45.6)	<.001
Patient	67/67 (100)	60/63 (95.2)	.071
POSAS researchers, mean (SD)	Overall opinion	Overall opinion	
Observer 1	2.3 (1.8)	3.4 (1.9)	.001
Observer 2	2.7 (2.0)	4.2 (2.6)	<.001
Patient	2.0 (1.7)	2.4 (2.0)	.282

POSAS, Patient and Observer Scar Assessment Scale; SD, standard deviation.

Table IV. Patient reported satisfaction of the allocated treatment

Patient satisfaction	Curettage and imiquimod	Surgery
I would undergo this treatment again, n (%)		
I agree	57 (85.1)	63 (95.5)
I do not agree	8 (11.9)	2 (3)
I do not know	2 (3)	1 (1.5)
I would recommend this treatment to others, n (%)		
I agree	59 (88)	57 (86.4)
I do not agree	3 (4.5)	2 (3)
I do not know	5 (7.5)	7 (10.6)
I am satisfied about the cosmetic result, n (%)		
I agree	59 (88)	64 (97)
I do not agree	4 (6)	1 (1.5)
I do not know	4 (6)	1 (1.5)

may threaten external validity. A second limitation is that no adjustment was possible for the slight imbalances in the baseline characteristics between the randomized groups because of the lack of treatment failures in the excision group. Randomization ensures that the allocation of treatment to patients is left purely to chance, but there is no guarantee that all baseline characteristics will be evenly distributed between groups.¹⁶ A third limitation is the 1-year follow-up period. Longer observation is required to ensure that late recurrences are not missed. However, the 5-year results in the SINS study showed that most treatment failures were identified early within the first year after treatment and that recurrences of low-risk BCC after topical imiquimod did not appear to be difficult to treat.⁶

Overall, in the treatment decision for nBCC the benefits of curettage and imiquimod should be weighed against the decrease in effectiveness compared with excision. Given the still high efficacy and the fairly indolent growth pattern, curettage and imiquimod could still be a valuable treatment option in nBCC, with the possibility to decrease the

workload in clinical practices. It cannot, however, replace surgical excision as the first treatment choice.

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