Optical coherence tomography versus punch biopsy for diagnosis of basal cell carcinoma

Optical coherence tomography versus punch biopsy for diagnosis of basal cell carcinoma: a multicentre, randomised, non-inferiority trial

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Summary

Background Punch biopsy is the gold standard for diagnosis and subtyping of basal cell carcinoma. The aim of this study was to assess whether use of optical coherence tomography (OCT), a non-invasive imaging tool, might avoid the need for biopsy.

Methods In a multicentre, randomised, non-inferiority trial, patients (aged ≥18 years) with an indication for biopsy of a suspected basal cell carcinoma outside the H-zone (high-risk zone) of the face were randomly assigned (1:1) to receive either OCT or punch biopsy (regular care) via a web-based randomisation system. Patients were enrolled from three participating centres in the Netherlands: Maastricht University Medical Centre+, Catharina Hospital Eindhoven, and Zuyderland Medical Centre Heerlen. Stratification factors for randomisation were participating centre and the grade of clinical basal cell carcinoma suspicion (high *vs* low). The primary endpoint was the proportion of patients free from a recurrent or residual lesion (malignant or premalignant) 12 months after treatment. Modified intention-to-treat and per-protocol analyses were conducted, with a predefined non-inferiority margin of –10%. This trial is registered with ClinicalTrials.gov number, NCT03848078, and is complete.

Findings Between Feb 25, 2019, and Sept 2, 2020, 598 patients were enrolled and randomly assigned to either the regular care group (n=299) or the OCT group (n=299). Data on the primary endpoint were available in 553 patients (n=268 in the regular care group, n=285 in the OCT group). After median follow-up of 12·7 months (IQR 11·2–14·1) in the OCT group and 12·6 months (10·8–14·3) in the regular care group, 253 (94%) of 268 patients in the OCT group and 266 (93%) of 285 patients in the regular care group were free from recurrent or residual lesions (malignant or pre-malignant) 12 months after treatment. According to our modified intention-to-treat analysis, the absolute difference (OCT *vs* regular care) was 1·07% (95% CI –2·93 to 5·06; one-sided p=0·30), with the lower limit of the 95% CI not exceeding the predefined non-inferiority margin of –10%. Per-protocol analyses led to proportions free from a residual or recurrent lesion (premalignant or malignant) of 95% (250 of 263) in the OCT group and 94% (262 of 278) in the regular care group, and an absolute difference of 0·81% (95% CI –2·98 to 4·60; one-sided p=0·34).

Interpretation OCT-guided diagnosis and treatment of basal cell carcinoma is non-inferior to regular care punch biopsy. Implementation of OCT for diagnosis of basal cell carcinoma could reduce the number of consultations and invasive procedures.

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Introduction

In White populations, one in five people will develop a basal cell carcinoma.[1,2] For diagnosis of lesions suspected to be basal cell carcinoma, guidelines recommend a punch biopsy to guide the decision on optimal treatment.[3,4] Histopathological diagnosis is important to distinguish between basal cell carcinoma and non-basal cell carcinoma lesions and to determine the histopathological subtype. For superficial basal cell carcinoma, topical therapy might be prescribed; however, for non-superficial basal cell carcinoma, the width of resection margins or an indication for Mohs' micrographic surgery is based on the subtype. Besides the inconvenience of a biopsy, awaiting histopathological examination causes treatment delay. Optical coherence tomography (OCT) has emerged as a promising non-invasive tool for basal cell carcinoma diagnosis, generating real-time, in-vivo, cross-sectional images of tissue microarchitecture with a depth of 1·0–1·5 mm.[5] OCT is based on light interferometry: the interference of two optical beams reflected by tissue produces distinguishable shades in the black and white spectrum, which allows the identification of morphological basal cell carcinoma characteristics.[6]

OCT might avoid the need for biopsy if an OCT diagnosis of basal cell carcinoma and subtype can be made with high confidence.[7–9] A treatment plan can be made immediately

Research in context

Evidence before this study

We searched PubMed, Cochrane databases, reference lists of papers on optical coherence tomography (OCT) and basal cell carcinoma, controlled-trials.com, ClinicalTrials.gov, and the UK NHS centre for reviews and dissemination on March 6, 2018, for articles published in English, with no date limits. We used the search terms "optical coherence tomography or OCT", "basal cell carcinoma or BCC", "specificity", and "sensitivity". Inclusion criteria were populations of patients with a skin lesion suspected to be basal cell carcinoma, histological assessment with a punch biopsy or excision used as gold standard, and that sensitivity and specificity estimates could be derived from the study. Five prospective cohort studies fulfilled these inclusion criteria and were judged on the basis of Quality Assessment of Diagnostic Accuracy Studies-2 criteria. None of these studies had a low risk of bias, mostly due to the absence of transparency concerning patient flow and methods for the estimation of sensitivity and specificity. The reference standard was judged as unclear in all studies because the gold standard was not defined clearly or because it was not reported whether an independent, experienced dermatopathologist assessed the histopathological slides. Our review showed that the literature demonstrates promising results regarding the use OCT-guided diagnosis of basal cell carcinoma to justify dermatologists' interest in this technique. In December, 2018, a Cochrane systematic review on the use of OCT for diagnosing skin cancer concluded that conventional OCT might have a role in the diagnosis of basal cell carcinoma in clinically challenging lesions. The meta-analysis showed a higher sensitivity and specificity for OCT than for visual inspection and dermoscopy; however, due to a small number of studies and varying methodological quality, implications to guide clinical practice could not be drawn yet. Appropriately designed prospective comparative studies are needed.

Added value of this study

To our knowledge, this study is the only clinical trial so far that evaluates whether OCT-guided diagnosis and treatment of clinically suspected basal cell carcinoma is non-inferior to punch biopsy (ie, regular care) in terms of clinical effectiveness and cost-effectiveness.

Implications of all the available evidence

Our findings and the evidence generated justify OCT being considered for inclusion in international guidelines for basal cell carcinoma diagnosis. Implementation of OCT requires the reorganisation of current clinical practices, wherein a punch biopsy with 1 week waiting time for the results can be replaced by a one-stop-shop approach in around two-thirds of suspected basal cell carcinoma cases. An important condition for the successful implementation of OCT in clinical practice is sufficient training. It is crucial that criteria be set for adequate diagnostic performance and for the time and training required to achieve good diagnostic performance.

and a diagnostic biopsy would only be taken in case of doubt. With this strategy, it has been reported that a punch biopsy could be omitted in 30–40% of patients, with low risk of misclassification.[7–10] There is a small risk that non-basal cell carcinoma lesions are misdiagnosed as basal cell carcinoma or that nodular or aggressive basal cell carcinoma subtypes are underdiagnosed as superficial basal cell carcinoma by OCT.

To date, it remains unclear to what extent misclassifications would result in a higher risk of treatment failure. We, therefore, conducted a randomised, controlled trial with the aim of ruling out that OCT-guided diagnosis and treatment results in an unacceptable increase in treatment failures when compared with regular care.

Methods

Study design and participants

For this multicentre, prospective, randomised, non-inferiority trial, we included consecutive patients who visited the dermatology departments of one academic (Maastricht University Medical Centre+, Maastricht, the Netherlands) and two general Dutch hospitals (Catharina Hospital, Eindhoven, the Netherlands; Zuyderland Medical Centre, Heerlen, the Netherlands). Eligible participants were adults (aged ≥18 years) with an indication for biopsy of a lesion with basal cell carcinoma in the differential diagnosis. This indication was based on clinical and dermoscopical examination, including lesions in which basal cell carcinoma diagnosis was considered—but where another benign, premalignant, or malignant diagnosis was also possible—as well as lesions with a high suspicion for basal cell carcinoma, but where doubt remained about the basal cell carcinoma subtype. The grading given to the certainty with which basal cell carcinoma was suspected (clinically and dermoscopically) was based on the treating physician's judgement before randomisation. We excluded patients in whom the diagnosis of basal cell carcinoma was so evident that the lesion could be treated directly without the need for biopsy, patients with lesions located in the H-zone (high-risk zone) of the face or with locally advanced basal cell carcinoma, and patients who were unable to sign informed consent documents.

See Online for appendix

All patients provided written informed consent before randomisation. The trial was performed according to the principles of the Declaration of Helsinki, and the protocol and two amendments were approved by the Medical Ethical Committee of Maastricht University Medical Centre+. The study protocol and statistical analysis plan are available in the appendix.

Randomisation and masking

Patients were enrolled by their treating physician and were randomly assigned (1:1) to one of two diagnostic

strategies: the OCT group or the regular care (punch biopsy) group. Randomisation was stratified by participating centre and by the grade of clinical basal cell carcinoma suspicion (high *vs* low). Randomisation schemes were made with an online computer-generated list using block sizes of four, six, and eight. The randomly assigned treatment allocations were revealed to the investigator using an online system (Castor electronic data capture system).

The investigator who assessed all OCT scans (FA) set the indication for treatment together with the supervising dermatologist (KM, TB, or JPHMK). Both individuals were aware of the group assignment, but were unaware of the biopsy results in case OCT diagnosis was made with high confidence. Due to the nature of the procedure, patients could not be masked to group assignment. Evaluation of the treated site at 12 months was done by the patients' own dermatologist who was unaware of group assignment. The dermatopathologists of the study centre where the patient was recruited, who were responsible for histopathological examination, were masked to the OCT results. Analysis of the data was performed by a statistician who was unaware of the coding for randomised groups.

Procedures

In the OCT group, one investigator (FA) made OCT scans of all lesions. The area that seemed most aggressive based on clinical and dermoscopic examination was marked as the biopsy area and centred in the OCT scan. OCT scans were made with a Vivosight Multi-beam Swept-Source Frequency Domain OCT scanner (Michelson Diagnostics, Maidstone, Kent, UK; resolution <7·5 mm lateral, <5 mm axial; depth of focus 1·0 mm; scan area 6×6 mm²). All OCT images were coded and saved anonymously. The investigator evaluated the OCT scan and decided whether the lesion was a basal cell carcinoma or not, based on established morphological basal cell carcinoma features.[6] Investigator training consisted of a literature review on OCT in dermatology, attendance of an OCT convention,[11] and assessment of more than 500 scans within a period of 4 months.

The level of confidence in basal cell carcinoma diagnosis was documented using a 5-point Likert-scale (appendix p 1), scored from 0 to 4, where a score of 4 indicated high confidence in the OCT diagnosis and basal cell carcinoma subtype. For diagnoses with a score of 4, the basal cell carcinoma subtype was further subclassified as superficial, nodular, or aggressive, and the treatment strategy was discussed during the same visit. If non-invasive treatment was indicated and preferred, it was immediately prescribed and, if surgery was indicated, the procedure was scheduled. In the OCT group, diagnosis and treatment was based on OCT only if the diagnosis of basal cell carcinoma and subtype could be made with high confidence. In patients with low confidence scores (0–3), a 3 mm punch biopsy was obtained and the histopathological result was awaited to determine diagnosis and treatment. For safety reasons, a punch biopsy was also taken in patients with a high confidence OCT-guided diagnosis, and one experienced dermatologist (per centre) checked the results and intervened only if treatment based on OCT would seriously compromise patient safety.

In the regular care group, diagnosis and treatment was always based on a 3-mm punch biopsy obtained under local anaesthesia. After embedding the biopsy in paraffin, histology slides were made and stained with haematoxylin and eosin, and were assessed by a dermatopathologist. The diagnosis was discussed with the patient via a telephone consultation by the investigator.

For more on **Castor** see https://www.castoredc.com/

A standardised treatment protocol was used for patients in both groups. Patients with a diagnosis of superficial basal cell carcinoma were offered the choice between imiquimod 5% cream or surgical excision. Patients with a diagnosis of nodular or aggressive basal cell carcinoma were treated with surgical excision or Mohs' micrographic surgery. For alternative diagnoses, treatment was based on the guideline for that specific diagnosis.[12,13] Alternative treatments were allowed if there were valid reasons to choose for another therapy.

Follow-up visits were scheduled at 12 months after the end of treatment, with a time window of 9–18 months due to the COVID-19 pandemic. After non-invasive treatment, an extra consultation took place at 3–4 months after treatment to evaluate whether there was complete tumour clearance. A dermatologist, who was unaware of group allocation, evaluated the treated site at 12 months after treatment. Clinically suspected recurrence was verified by histopathological examination.

We conducted a cost-effectiveness analysis that followed the Dutch guidelines for cost-calculations in health care and was performed from a health-care perspective with a time horizon of 12 months.[14] The reason for using the health-care perspective was that productivity loss and out-of-pocket costs, such as travel costs or use of services outside health care (such as medication), were expected to be minimal.

For the cost-analysis, a distinction was made between the diagnostic, treatment, and post-treatment phase. Resource use related to the diagnostic phase consisted of an outpatient visit, a clinical photograph, an OCT scan, a punch biopsy, and a telephone consultation. A punch biopsy was always included in the economic evaluation for the regular care group. For the OCT group, costs of a biopsy were only included if basal cell carcinoma diagnosis could not be made using OCT with high confidence to be representative of real-world clinical practice and avoid trial-induced costs. If OCT diagnosis was certain, no telephone consultation was needed because diagnosis and treatment were immediately discussed. For both the OCT and regular care group, extra visits or telephone consultations related to questions about therapy were registered.

Cost prices were obtained from the hospital financial department or the Dutch manual for costing research.[14] The cost prices and calculations used are summarised in the appendix (p 1). All resource use data were collected from the hospital information systems of the participating hospitals. Because all costs and effectiveness data were collected within 1 year, no discounting was applied. All costs were indexed to 2019.

Outcomes

The primary outcome was the proportion of patients remaining free from recurrent or residual lesion (premalignant or malignant) at 12 months after treatment. We considered a follow-up period of 12 months long enough to capture most recurrences, given that recurrences after non-invasive treatment predominantly appear within the first year.[15] Secondary outcomes were the proportion of patients in whom punch biopsy could be avoided (OCT diagnosis with confidence level 4), the diagnostic accuracy of high confidence OCT diagnosis, the frequency of misclassifications, and the area under the receiver operating characteristic curve as a measure of the overall diagnostic performance of OCT. The histopathological result from the punch biopsy was used as the gold standard. We conducted a discrete choice experiment to examine patient preferences for OCT or punch biopsy as a diagnostic strategy; this extensive research is published elsewhere.[16]

For more on **EuroQoL** see http://www.euroqol.org/

For the cost-effectiveness analysis, the main outcome was the incremental cost-effectiveness ratio, expressed as the incremental costs per additional patient free from a recurrent or residual skin lesion (pre-malignant or malignant) 12 months after treatment. This ratio is calculated as the difference in costs divided by the difference in effectiveness (ie, recurrence-free rate) at 12 months follow-up.

The secondary outcome for our economic evaluation was costs per quality-adjusted life-year (QALY), based on the recommendations of the Dutch manual for costing.[14] QALYs were calculated using scores on the EuroQoL five-dimensional, five-level (EQ-5D-5L) questionnaire, a generic health-related quality of life questionnaire that includes five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The Dutch tariff for the EQ-5D-5L was used to value the health states as experienced by patients.[17]

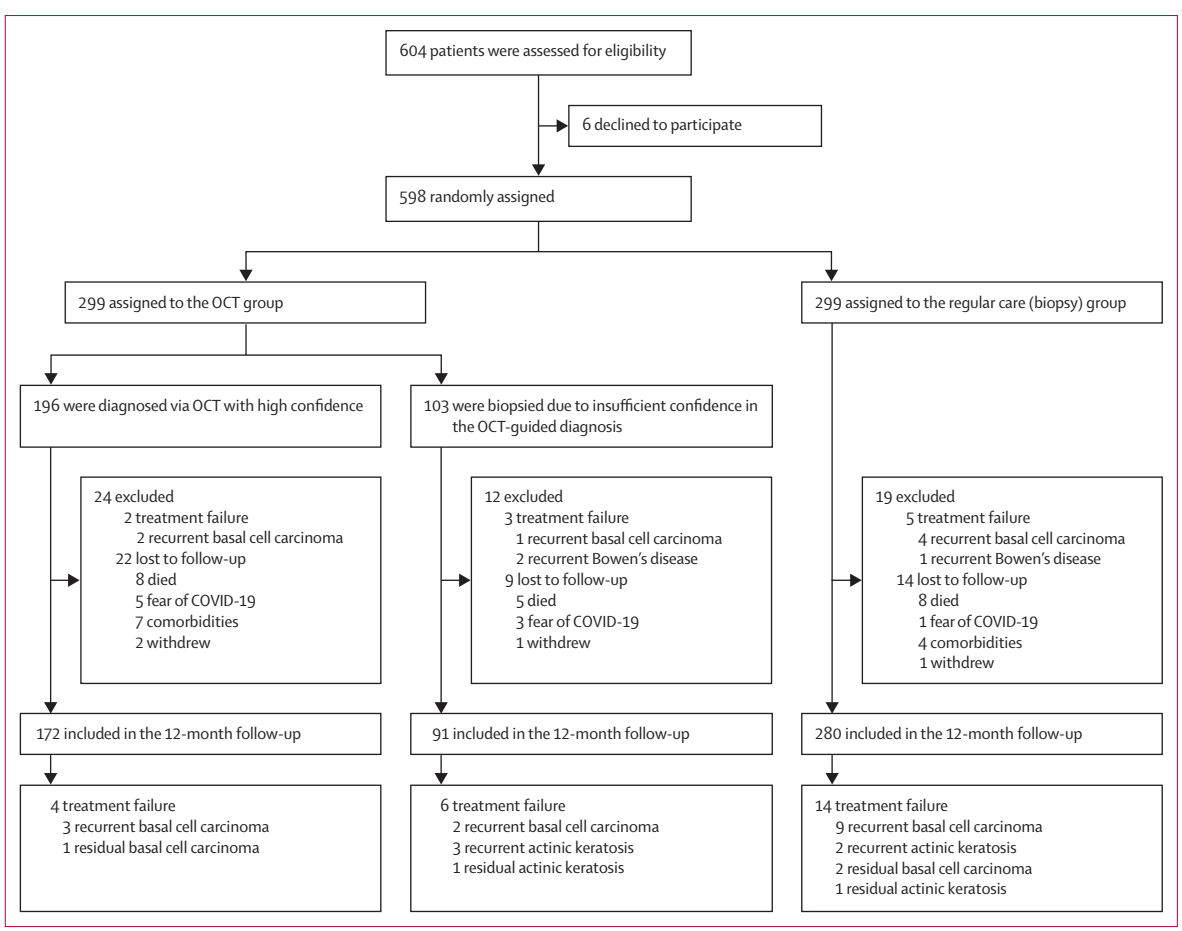

Figure: **Trial profile**
OCT=optical coherence tomography.

Statistical analysis

For the sample size calculation, we assumed that the proportion of patients free from a recurrent or residual lesion (premalignant or malignant) 12 months after treatment in the regular care group would be 85%. To obtain 90% confidence that the lower limit of a two-sided 95% CI will exclude a difference in favour of the regular care group of more than 10% (our non-inferiority margin), 538 (269 in each group) patients were required. Accounting for a 10% loss to follow-up, 598 patients were required for inclusion. Patients were not assessable for inclusion when they declined to participate. One-sided p values of 2·5% (corresponding with two-sided p values of 5%) were considered to indicate statistical significance. Non-inferiority of OCT versus regular care was evaluated by calculating the absolute difference in the proportions of patients free from a recurrent or residual lesion (premalignant or malignant) at 12 months after treatment with a two-sided 95% CI and one-sided p value (calculated via χ^2 test with OpenEpi, version 3).

Modified intention-to-treat and per-protocol analyses were both performed. Although the protocol planned for an intention-to-treat analysis, a modified intention-to-treat analysis was done because only patients who were randomly allocated to a group and for whom the primary outcome was available could be included in the analysis. Excluded from the per-protocol population were patients with a lesion (premalignant or malignant) who did not start treatment. One lesion per patient was included to ensure independence of observations.

Diagnostic performance in patients with a high confidence OCT-guided diagnosis was expressed as sensitivity, specificity, positive predictive value, and negative predictive value, with corresponding 95% CIs. Receiver operating characteristic curves were constructed to visualise the sensitivity and specificity at alternative thresholds for a positive test result, and the area under the curve with 95% CI was calculated as a measure for the overall diagnostic performance of OCT. The cost-effectiveness analysis was performed according to the modified intention-to-treat principle. Since cost data are generally skewed, a bootstrap analysis (1000 samples) was performed to generate 95% CIs around the difference in mean costs and to quantify the uncertainty surrounding the cost-effectiveness ratio. The bootstrap method estimates the sampling distribution of a statistic through a large number of simulations, based on sampling with replacement.[18] Results of the bootstrap analysis are presented in cost-effectiveness planes and acceptability curves (see appendix p 5 for details).

The bootstrap analysis was done using Microsoft Excel 2016. To test the robustness of the cost-effectiveness results, four univariate post-hoc sensitivity analyses were conducted: first, a per-protocol analysis in which patients who did not start treatment for a skin lesion (pre-malignant or malignant) were excluded; second, a sensitivity analysis in which OCT costs were calculated based on personnel costs of a dermatologist instead of a physician (meaning that OCT costs are increased); third, a sensitivity analysis in which we doubled the OCT costs to account for an unexpected rise in costs; and fourth, a sensitivity analysis in which we set the percentage of biopsies that could be omitted at 40%, since previous studies reported that an OCT diagnosis of basal cell carcinoma could be made with high confidence (and thus biopsies can be omitted) in 30–40% of patients.[8–10] For this fourth sensitivity analysis, we assumed that diagnostic accuracy—and thereby the risk of misclassifications and associated risk of recurrent basal cell carcinoma—did not change, although these values can be correlated to level of confidence in diagnoses of an OCT assessor.

To estimate the costs per QALY, we performed a cost-utility analysis using a regression-based correction

	OCT group (n=299)	Regular care group (n=299)
Age, years		
Median (IQR)	72 (62–80)	73 (63–80)
Sex		
Male	164 (55%)	162 (54%)
Female	135 (45%)	137 (46%)
Localisation		
Head or neck	94 (31%)	97 (32%)
Upper anterior chest	37 (12%)	33 (11%)
Trunk	89 (30%)	87 (29%)
Extremities	79 (26%)	82 (27%)
Histological diagnoses		
Basal cell carcinoma	225 (75%)	215 (72%)
No basal cell carcinoma	74 (25%)	84 (28%)
Basal cell carcinoma subtypes		
Superficial	80/225 (36%)	73/215 (34%)
Nodular	113/225 (50%)	106/215 (49%)
Aggressive (morpheaform or micronodular)	32/225 (14%)	36/215 (17%)
Other diagnoses (non-basal cell carcinoma)		
Benign lesion*	34/74 (11%)	37/84 (12%)
Actinic keratosis	24/74 (8%)	23/84 (8%)
Bowen's disease	9/74 (3%)	18/84 (6%)
Squamous cell carcinoma	5/74 (2%)	4/84 (1%)
Superficial spreading malignant melanoma	1/74 (<1%)	0
Atypical fibroxanthoma	1/74 (<1%)	0
Primary cutaneous follicle centre lymphoma	0	1/84 (<1%)
Sebaceous carcinoma	0	1/84 (<1%)

Data are n (%) or n/N (%) unless otherwise stated. *Including sebaceous gland hyperplasia or adenoma (or both), dermatofibroma, dermal nevus, seborrhoic keratosis, scar, benign lichenoid keratosis, folliculitis, neurofibroma, trichofolliculoma, venous stasis dermatitis, sclerosing dermatitis, excoriation, dilated hair follicle, angioma, chronic inflammation, eczema, apocrine hidrocystoma, epidermoid cyst, blue nevus, halo nevus, solar elastosis, solar lentigo, verruca vulgaris, lichen planopilaris, lichenoid dermatitis, nodular prurigo, and dermal mucinosis.

Table 1: **Baseline characteristics**

	OCT group (n=299)	Regular care group (n=299)	p value
Diagnosis			
Based on OCT	66% (196/299)	0	..
Based on biopsy	34% (103/299)	100% (299/299)	..
Misclassifications			
Frequency*	18% (36/196)	..	..
Type			..
Histological non-basal cell carcinoma as basal cell carcinoma	2% (4/196)	..	..
Classified as superficial basal cell carcinoma (treated with imiquimod), n	2	..	..
Classified as other subtype (treated with excision), n	2	..	..
Histological superficial basal cell carcinoma as other subtype	35% (25/72)	..	..
Treated with imiquimod, n	1	..	..
Treated with excision, n	24	..	
Histological non-superficial basal cell carcinoma as superficial basal cell carcinoma	6% (7/120)	..	..
Treated with imiquimod, n	4	..	..
Treated with excision, n	3	..	..
Treatment with imiquimod			
Superficial basal cell carcinoma†	45% (36/80)	51% (37/73)	0·49
Nodular basal cell carcinoma	5% (6/113)	1% (1/106)	0·08
Aggressive basal cell carcinoma	..	..	..
Surgical treatment			
Superficial basal cell carcinoma	55% (44/80)	42% (31/73)	0·13
Nodular basal cell carcinoma‡	92% (104/113)	96% (102/106)	0·21
Aggressive basal cell carcinoma§	100% (32/32)	94% (34/36)	0·28
Actinic keratosis¶	0	4% (1/23)	0·49
Bowens' disease	44% (4/9)	44% (8/18)	1·00
Squamous cell carcinoma‖	80% (4/5)	100% (4/4)	0·56
Other malignancies	100% (2/2)	100% (2/2)	..
Frequency of recurrence or residual lesion (premalignant or malignant)			
All lesions	6% (15/268)	7% (19/285)	0·61
Misclassified lesions	0	..	..

Numbers and percentages are presented per randomised group. Data are % (n/N) unless otherwise stated. OCT=optical coherence tomography. *Misclassification: OCT-guided diagnosis versus punch biopsy diagnosis. †In the regular care group, three superficial basal cell carcinoma lesions were treated with 5-fluorouracil, one did not begin imiquimod treatment, and one switched from imiquimod to methyl aminolevulinate photodynamic therapy. ‡In the OCT group, three patients with nodular basal cell carcinoma did not begin treatment. In the regular care group, three patients with nodular basal cell carcinoma did not begin treatment. §In the regular care group, two patients with aggressive basal cell carcinoma did not begin treatment. ¶Actinic keratosis lesions were treated with cryotherapy (OCT group: n=18 [n=2 did not begin treatment], regular care group: n=12 [n=5 did not begin treatment]), 5-fluorouracil (OCT group: n=1 [n=1 did not begin treatment], regular care group: n=5), or imiquimod (OCT group: n=2). ‖One patient with squamous cell carcinoma in the OCT group did not begin surgical treatment since the lesion was radically removed via punch biopsy.

Table 2: **Comparison of patient outcomes, by study group**

method to correct for baseline differences in utility scores.[19]

SPSS (version 25) and STATA (version 14) were used for statistical analyses. This trial is registered with ClinicalTrials.gov, NCT03848078.

Role of the funding source

One of the funders of the study (Netherlands Organization for Health Research and Development, known as ZonMw) was involved in the study design. Neither of the funders had a role in data collection, data analysis, data interpretation, or writing of the report. publication.

Results

Between Feb 25, 2019, and Sept 2, 2020, 604 patients were assessed for eligibility (figure). 598 patients from three participating centres (Maastricht University Medical Centre+ [n=344], Catharina Hospital [n=176] and Zuyderland Medical Centre [n=78]) were enrolled and randomly assigned to either the regular care group (n=299) or the OCT group (n=299). According to histopathology, 225 (75%) of 299 in the OCT group and 215 (72%) of 299 in the regular care group had basal cell carcinoma. The distribution of baseline characteristics was similar between the two groups (table 1). Data on race or ethnicity were not collected. In the OCT group, a high confidence diagnosis of basal cell carcinoma and basal cell carcinoma subtype could be made in 196 (66%) of 299 patients. The remaining 103 patients (34%) still required a biopsy to establish a diagnosis. 36 (45%) of 80 patients in the OCT group and 37 (51%) of 73 patients in the regular care group received non-invasive treatment (imiquimod) for histologically superficial basal cell carcinoma (table 2).

Median follow-up was 12·7 months (IQR 11·2–14·1) for the OCT group and 12·6 months (10·8–14·3) for the regular care group. 45 patients (8%) did not attend the planned 12-month follow-up visit for various reasons (figure). Loss-to-follow-up, partly attributable to COVID-19-related issues, was more common in the OCT group (31 [10%]) than in the regular care group (14 [5%]), which is probably due to chance. In most patients (OCT group: ten [67%] of 15 patients, regular care group: 16 [84%] of 19 patients) with clinical suspicion of a residual or recurrent lesion (premalignant or malignant), histopathological verification was obtained, with the exception of eight patients (OCT group: n=5, regular care group: n=3) who considered a biopsy too burdensome.

The modified intention-to-treat analysis was based on 553 enrolled patients for whom data on the primary endpoint (patients free from a recurrent or residual lesion [pre-malignant or malignant]) were available (268 in the OCT group and 285 in the regular care group). 1 year after treatment, 253 (94%) of 268 patients in the OCT group were free from a recurrent or residual lesion (pre-malignant or malignant) versus 266 (93%) of 285 in the regular care group (figure). The absolute difference between the groups (OCT–regular care) was 1·07% (95% CI –2·93 to 5·06, one-sided p=0·30). Among patients with residual or recurrent lesions (premalignant or malignant), nine of 15 patients had a malignant lesion in the OCT group versus 15 of 19 in the regular care group.

For the per-protocol analysis, 12 patients who did not start treatment were excluded. Five patients (two in the OCT group and three in the regular care group) had

residual basal cell carcinoma or actinic keratosis at 12 months follow-up. In the remaining seven patients (OCT group: n=3, regular care group: n=4), the lesion was no longer visible at follow-up. Per-protocol analyses led to proportions free from a residual or recurrent lesion (premalignant or malignant) of 95% (250 of 263) in the OCT group and 94% (262 of 278) in the regular care group, and an absolute difference of 0·81% (95% CI –2·98 to 4·60; one-sided p=0·34). Eight of 13 patients in the OCT group and 13 of 16 patients in the regular care group had a malignant lesion. As the lower limit of the 95% CI does not exceed the non-inferiority margin of –10% in either the modified intention-to-treat or per-protocol analysis, OCT-guided diagnosis and treatment was non-inferior to regular care.

The area under the receiver operating characteristic curve, which is a measure of the diagnostic performance of OCT was 95·2% (95% CI 92·1–98·3) and the receiver operating characteristic curve is presented in the appendix (p 8).

In this study, the ability of a high confidence OCT-guided diagnosis to discriminate between basal cell carcinoma and non-basal cell carcinoma lesions and between superficial and more aggressive basal cell carcinoma subtypes is of primary interest. The results of our comparison of high confidence diagnosis by OCT with histopathological diagnosis are presented in tables 3 and 4. Of the 225 histologically verified basal cell carcinomas in the OCT group, 192 basal cell carcinomas were detected by high confidence OCT-guided diagnosis, corresponding to a sensitivity of 85·3% (95% CI 82·9–86·5). The specificity was 94·6% (87·1–98·2), given that 70 of 74 histological non-basal cell carcinoma lesions were diagnosed as a non-basal cell carcinoma lesion by OCT (table 3). Among the 192 basal cell carcinomas that were identified by OCT, OCT correctly identified 47 of 72 histologically superficial basal cell carcinomas (specificity 65·3%, 95% CI 57·4–70·4) and 113 of 120 other subtypes (sensitivity 94·2%, 89·5–97·2). With OCT, absence of basal cell carcinoma was predicted in 103 lesions, of which 70 were histologically confirmed non-basal cell carcinoma, corresponding to a negative predictive value of 68·0% (95% CI 62·6–70·6). With OCT, presence of basal cell carcinoma was predicted in 196 lesions, of which 192 were histologically confirmed basal cell carcinoma, corresponding to a positive predictive value of 98·0% (95% CI 95·1–99·3). Four lesions were non-basal cell carcinoma lesions according to histopathological diagnosis: actinic keratosis (n=2), Bowen's disease (n=1), and osteoma cutis (n=1). The two actinic keratosis lesions were classified as superficial basal cell carcinoma by OCT and treated with imiquimod 5% cream, and the other two lesions were classified as non-superficial basal cell carcinoma and were treated with surgical excision. The 192 basal cell carcinomas that were correctly identified as basal cell carcinoma by OCT consisted, histologically, of 72 superficial basal cell carcinomas and 120 non-superficial basal cell carcinomas. With OCT, 56 basal cell carcinomas were classified as superficial basal cell carcinoma; however, seven of these were non-superficial basal cell carcinoma according to histopathology (table 4). Four of these seven non-superficial basal cell carcinoma subtypes were treated with imiquimod 5% cream, and none of these four patients developed a recurrent basal cell carcinoma 12 months after treatment. Three of the seven patients preferred surgical excision. 140 lesions were classified as non-superficial basal cell carcinoma by OCT, but 25 of 140 lesions were superficial basal cell carcinoma on histology (table 4). Based on the OCT diagnosis, 24 of these 25 basal cell carcinomas were treated with surgical excision. The remaining patient was treated with imiquimod. A non-superficial basal cell carcinoma was diagnosed in 13 of the 24 available excision specimens. One patient with a non-superficial basal cell carcinoma on OCT preferred imiquimod treatment because he had multiple basal cell carcinomas. However, the basal cell carcinoma was resistant to treatment and histology of the residual tumour confirmed the presence of non-superficial basal cell carcinoma. Overall, high confidence OCT-guided diagnosis resulted in an incorrect diagnosis in 36 patients, but none of these patients had a residual or recurrent lesion (premalignant or malignant; table 2). One patient in the OCT group had a melanoma, which was clinically highly suspected to be basal cell carcinoma but was correctly identified with OCT as a non-basal cell carcinoma lesion with an indication for biopsy.

Results of the cost analysis for the OCT group and the regular care group are shown in the appendix (p 3). The total mean costs of the diagnostic phase were significantly lower for the OCT group (€233) than in the regular care

	Basal cell carcinoma	Non-basal cell carcinoma	Total
Basal cell carcinoma	192	4	196
Non-basal cell carcinoma	33	70	103
Total	225	74	299

Data are n. BCC=basal cell carcinoma. OCT=optical coherence tomography.

Table 3: **The ability of high confidence OCT-guided diagnosis (Likert score 4) to discriminate between BCC and non-BCC lesions**

	Superficial basal cell carcinoma	Non-superficial basal cell carcinoma	Non-basal cell carcinoma	Total
Superficial basal cell carcinoma	47	7	2	56
Non-superficial basal cell carcinoma	25	113	2	140
Total	72	120	4	196

Data are n. OCT=optical coherence tomography.

Table 4: **The ability of high confidence OCT-guided diagnosis (Likert score 4) to discriminate between superficial and non-superficial basal cell carcinoma subtypes**

group (€308). There were no significant differences in treatment, post-treatment costs, and total mean costs between the two groups (appendix p 3).

In the modified intention-to-treat analysis, the incremental cost-effectiveness ratio for OCT-guided diagnosis and treatment compared with punch biopsy indicates that OCT is a cost-effective strategy due to OCT having lower costs (€689 *vs* €758) and slightly higher effectiveness (0·94 *vs* 0·93) than punch biopsy (appendix p 3).

Bootstrap results are in the appendix (p 4) and show that the majority of the cost-effectiveness ratios indicate OCT as more effective and less costly than regular care. The acceptability curve (appendix p 4) for the cost-effectiveness ratios that suggest cost savings but less effectiveness of OCT shows that for threshold values of €500–5000, the probability of OCT-guided diagnosis and treatment being more cost-effective than punch biopsy is higher than 80%. The appendix (pp 4–6) presents the results of the sensitivity cost-effectiveness analyses analyses. The results of the cost-utility analysis show that mean costs were lower in the OCT group than in the regular care group and mean QALYs were slightly higher (appendix p 7), suggesting that an OCT-guided diagnostic strategy is cost-effective when compared with regular care (cheaper and with higher QALYs).

Discussion

The findings of this multicentre, randomised, non-inferiority trial show that OCT-guided diagnosis and treatment is non-inferior to regular care and does not compromise patient safety. In the OCT group, 253 (94%) of patients were free from a recurrent or residual lesion (premalignant or malignant) at 12 months follow-up compared with 266 (93%) patients in the regular care group. A high confidence OCT-guided diagnosis could replace a punch biopsy in 196 (66%) of 299 patients in the OCT group. None of the misclassifications that occurred had severe clinical implications, and none of the 15 recurrences in the OCT group were due to misclassification by OCT. The cost-effectiveness results indicate that OCT-guided diagnosis and treatment is a cost-effective strategy compared with regular care punch biopsy.

The largest risk of OCT-guided diagnosis is that a more aggressive malignancy (for example a melanoma) could be incorrectly diagnosed as basal cell carcinoma and treated non-invasively. In a study by Cheng and colleagues, one amelanotic melanoma was misclassified as superficial basal cell carcinoma.[7] In our study population, one patient in the OCT group had a melanoma, which was clinically highly suspected to be basal cell carcinoma but was correctly identified with OCT as a non-basal cell carcinoma lesion with an indication for biopsy.

Another risk is that misclassification of a non-superficial basal cell carcinoma as superficial basal cell carcinoma could result in the decision to treat such a lesion non-invasively, whereas excision is indicated for non-superficial lesions. However, the 5-year sustained clearance in low-risk nodular basal cell carcinoma treated with imiquimod cream is still 81%, with recurrences being detected early during follow-up.[20] For aggressive basal cell carcinoma, treatment with imiquimod cream seems more harmful than imiquimod treatment of nodular basal cell carcinoma. Imiquimod treatment for aggressive basal cell carcinoma has only been investigated in a small study, in which eight of 13 participants did not respond to treatment with imiquimod cream.[21] At a low-risk location (such as the trunk and extremities), resistant aggressive basal cell carcinomas can be easily retreated with surgical excision with wide margins, but such retreatment is more complex in the H-zone. There is also a risk that superficial basal cell carcinomas are misclassified as a more aggressive subtype, which results in a decision to treat the lesion with excision. Although surgery is an effective treatment for superficial basal cell carcinoma, the choice for a non-invasive treatment would then be wrongfully withheld.[4]

In this trial, 25 of 72 basal cell carcinomas diagnosed as superficial by punch biopsy were classified as non-superficial basal cell carcinoma by OCT diagnosis and treated with surgery. However, in 13 of these 25 patients, a non-superficial component was detected with histological examination of the excision specimen. This finding shows that OCT can also have an advantage over a 3-mm punch biopsy, in that the entire lesion is visualised instead of only 3 mm. It is known that biopsies, either punch or shave, do not always represent the entire lesion.[22,23]

In the OCT group, 55% of the basal cell carcinoma lesions were excised versus 42% in the regular care group; generally, more excisions were done for superficial basal cell carcinomas in the OCT group than in the regular care group. This imbalance is partly because of over classification. If the 25 basal cell carcinoma lesions over classified on OCT as non-superficial had been diagnosed as superficial, the number of superficial basal cell carcinoma lesions treated surgically could have been reduced to a minimum of 19 of 80 patients (table 2), which might affect the overall costs. However, because some patients chose to receive invasive treatment of superficial basal cell carcinoma—as was also the case in the regular care group—it is difficult to predict this impact. A second explanation for more patients with superficial basal cell carcinomas having received excision in the OCT group could be that neither the patient, nor the investigator and supervisor were masked to group assignment when deciding on the appropriate treatment. In the choice between non-invasive treatment or surgical excision, the potential uncertainty of the OCT scan might have influenced their preference for the certainty of excision.

OCT-guided diagnosis of basal cell carcinoma has potential advantages. From a patient's perspective, an OCT-guided strategy is an attractive option, because an

invasive procedure can potentially be avoided and basal cell carcinoma treatment can be initiated immediately.

Our findings show that OCT-guided diagnosis and treatment is a cost-effective strategy compared with regular care (punch biopsy). The bootstrap analysis showed that the majority of the cost-effectiveness ratios lie within the quadrant where OCT strategy is considered a dominant cost-effective strategy, leading to more effects and less costs. For the ratios in the southwest quadrant (less effective but cost saving), the acceptability curve shows the probability that the OCT strategy is cost-effective for different monetary threshold values. In this case, the value indicates the amount of money society is willing to accept for an additional patient with a residual or recurrent skin lesion (premalilgnant or malignant). However, since there is no threshold value for this, we considered that a threshold value should at least include the costs of treatment of a recurrent tumour. Using the total treatment costs of a surgical excision, minimum cost savings should be around €500. At a threshold of €500, the probability of OCT-guided diagnosis strategy being cost-effective is 99%. The acceptability curve shows that, even at much higher threshold values, the probability of OCT being cost-effective is around 80%.

In 196 (66%) of 299 patients, OCT diagnosis was certain and biopsy could be avoided. Savings made in the OCT group—ie, costs of a punch biopsy, histopathological examination, and a post-biopsy (telephone) consultation to discuss results—resulted in lower costs for the total OCT-guided strategy, despite both a biopsy and an OCT scan being obtained in 103 (34%) of 299 patients. Moreover, misclassification by OCT did not lead to higher treatment costs in the OCT group than in the regular care group. Sensitivity analyses showed that the OCT-guided strategy was still cost-effective compared with regular care in all four sensitivity analysis scenarios. The cost-utility analysis showed similar results to that of the cost-effectiveness analysis: mean costs were lower in the OCT group and mean QALYs were slightly higher than in the regular care group, suggesting that an OCT-guided diagnostic strategy is cheaper and leads to slightly higher QALYs than regular care. Cost prices used are specific to the Dutch health-care system and might differ per country, but data on resource use allow for determination of applicability per situation.

There are three key limitations to this study. First, the result strongly hinge on the OCT diagnoses made by a single, experienced physician, who had evaluated 500 scans before the start of the study. With OCT-guided diagnosis, a punch biopsy could be omitted in 66% of patients, which is more than could be achieved in previous studies (30–36% of biopsies avoided).[8,9] The diagnostic performance of an OCT assessor determines the risk of misclassifications and how often a biopsy can be omitted. Therefore, an important condition for successful implementation of OCT-guided diagnosis in clinical practice is sufficient training of OCT users.[24] To incorporate OCT in dermatological practice, it is crucial to set criteria for adequate performance and to quantify the time and training required to achieve such performance. In a former study, we have illustrated how cumulative sum analysis can be used to train novice assessors and to monitor the level of diagnostic performance over time.[24]

Second, this study excluded patients with large lesions or lesions located in the H-zone of the face because it was not yet known whether OCT-guided diagnosis and treatment could compromise patient safety. Basal cell carcinoma at this location has a higher risk of aggressive behaviour than other locations.[4] Furthermore, in the H-zone, surface areas are often convex or concave, which could affect the quality of the OCT image; therefore, more studies are needed to determine whether or not OCT is suitable in this subpopulation. Finally, although the majority (63–90%) of lesions are diagnosed by biopsy in the Netherlands, substantial variation exists between centres.[25,26] To increase the generalisability of results, this multicentre study was done in two general hospitals and one academic hospital. Generally, patients with lesions in whom a diagnosis of basal cell carcinoma is evident are directly treated without biopsy, and these lesions were excluded from this study. A 2021 study confirmed that, in this subgroup of patients, the additional diagnostic value of OCT is scarce.[27]

In summary, this trial shows that OCT-guided diagnosis and treatment is safe and non-inferior to regular care. In 66% of patients, a biopsy could be avoided, thus minimising treatment delay and avoiding an invasive procedure. Misclassifications did not have large clinical implications and did not lead to higher treatment costs in the OCT group than in the regular care (punch biopsy) group, but the risk of overtreatment or undertreatment must always be carefully weighed against the advantage of treatment without delay and less invasive procedures.

Contributors

FA, KM, NWJK-S, PJN, and BABE designed the protocol and literature search. FA, KM, NWJK-S, TB, and JPHMK coordinated the study. FA followed up patients and collected data. FA, NWJK-S, KM, PJN, and BABE wrote the report. FA, KM, NWJK-S, TB, JPHMK, SRPD, PJFQ, and GD enrolled patients. NWJK-S, SRPD, and PJFQ evaluated the results of punch biopsy and intervened if treatment based on OCT would seriously compromise patient safety. FA and PJN did the statistical analysis. FA and BABE did the cost-effectiveness analysis. VJLW and MAH performed histopathologic assessment. FA, KM, and PJN accessed and verified the data. All authors had access to all data in the study, and reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

The clinical study report is available upon request, after approval by the study principal investigator (KM) and corresponding author (FA). Deidentified individual participant data from this clinical trial and a data dictionary can be requested by filling out the data request form at https://dataverse.nl/dataset.xhtml?persistentId=doi:10·34894/VKERXP. Data will be available from 1 year after publication until 2 years after completion of the trial. The requests will be reviewed on a case-by-case basis. Data will be made available for researchers whose proposed use of the data has been approved by first or senior author of this manuscript and after approval of a proposal and with a signed data access agreement.

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