Optical Coherence Tomography for Noninvasive Diagnosis and Subtyping of Basal Cell Carcinoma

Optical Coherence Tomography for Noninvasive Diagnosis and Subtyping of Basal Cell Carcinoma: A Prospective Cohort Study

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Noninvasive diagnostic strategies such as optical coherence tomography (OCT) enable detailed examination of skin tissue architecture and have potential for identification and subtyping of basal cell carcinoma (BCC). To evaluate the additional diagnostic value of OCT, a prospective cohort study was performed in 182 patients with 250 lesions suspected for non-melanoma skin premalignancies requiring a biopsy. Accuracy of BCC diagnosis and subtype on the basis of clinical examination (CE) of patients was compared with that on the basis of OCT scans in conjunction with clinical images of lesions (cOCT). Confidence levels were recorded on a 5-point scale, where score 0 indicated absence of BCC and scores 1–4 indicated increasing suspicion of BCC. Diagnostic performance parameters were compared using histopathologic diagnosis as gold standard. The patient-based area under the receiver operating characteristic curve (AUC) increased from 85.6% for CE to 91.2% for cOCT ($P = 0.061$) and the lesion-based AUC from 82.7% to 91.3% ($P < 0.001$). When confidence scores 1–4 were defined as positive, patient-based specificity increased from 47.5% (CE alone) to 76.8% (cOCT) at similar sensitivity (97.6% and 95.2%, respectively). cOCT slightly improved the ability to discriminate between superficial and nonsuperficial BCC subtypes and seemed to be a valuable addition to CE alone in the diagnosis and subtyping of BCC.

Journal of Investigative Dermatology (2020) **140,** 1962–1967; doi:10.1016/j.jid.2020.01.034

INTRODUCTION

Skin cancer incidence is rising worldwide. The most common type of skin cancer is basal cell carcinoma (BCC). The general population has a lifetime risk of 16–20% to develop a BCC (Flohil et al., 2011). A punch biopsy is required to discriminate BCC from alternative diagnoses and to determine the histopathologic subtype (NVDV, 2015; Work Group et al., 2018). Knowledge of the histopathologic subtype is especially relevant in determining the optimal treatment. In case of superficial BCC, treatment with a topical therapy may be prescribed. In nonsuperficial BCCs, information of the subtype helps to determine the width of resection margins or to set an indication for Mohs' micrographic surgery. A punch biopsy is an invasive procedure that may be painful and carries a small risk of complications such as bleeding, scarring, and infection. Moreover, awaiting histologic assessment (approximately 1 week) causes treatment delay and can be stressful for patients. With the high volume of BCCs and potential drawbacks of invasive diagnostics, interest in noninvasive diagnostic methods is increasing. Optical coherence tomography (OCT) is an imaging technique that generates real-time in vivo cross-section images of tissue microarchitecture with a depth of 1.5–2 mm (Cheng and Guitera, 2015). OCT is based on light interferometry; the interference of two optical beams reflected by the tissue produces distinguishable shades in the black and white spectrum. Morphologic characteristics of BCC that may be distinguished on OCT images have been established in recent years (Hussain et al., 2015). Small studies coordinated by the OCT producers with selected patient populations have reported promising results with the use of OCT in diagnosing BCC and subtyping of superficial BCC (Cheng et al., 2016; Markowitz et al., 2015; Ulrich et al., 2015). A recent Cochrane Diagnostic Test Accuracy review on the accuracy of OCT for diagnosis of BCC stated that the small number of studies and varying methodologic quality make it impossible to guide practice (Ferrante di Ruffano et al., 2018). This prospective cohort study was initiated to investigate the ability of OCT in conjunction with clinical images (cOCT) to discriminate between (i) BCC and other diagnoses and (ii) superficial and nonsuperficial (nodular and aggressive) subtypes of BCC. An additional objective was to evaluate how often OCT scans, in conjunction with clinical images of lesions (cOCT) imaging, enabled making a diagnosis of BCC with high

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Abbreviations: AUC, area under the receiver operating characteristic curve; BCC, basal cell carcinoma; CE, clinical examination; cOCT, OCT scans in conjunction with clinical images of lesions; OCT, optical coherence tomography

Received 9 May 2019; revised 23 December 2019; accepted 13 January 2020; accepted manuscript published online 6 March 2020; corrected proof published online 10 April 2020

confidence and how many lesions would be misclassified if the punch biopsy would have been omitted in these cases.

RESULTS

A total of 182 patients with 250 lesions clinically suspicious for non-melanoma skin cancer or premalignancy were included in this study. All lesions were scanned by OCT and histopathologically verified by either punch biopsy or excision biopsy. If patients had multiple lesions, the first scanned lesion was selected for the analysis on patient level. The patient-based analysis therefore consisted of 182 lesions, of which 83 were BCCs and 99 were non-BCCs, corresponding to a BCC prevalence of 45.4%. Of those 83 BCCs, 26 (31.3%) were superficial BCCs, 36 (43.4%) nodular BCCs, and 21 (25.3%) aggressive BCCs. Patient and lesion characteristics are summarized in Table 1.

Ability to distinguish basal cell carcinoma from non–basal cell carcinoma

The area under the receiver operating characteristic curve (AUC) was 85.6% (95% confidence interval = 80.2–89.0%) for clinical examination (CE) alone and 91.2% (95% confidence interval = 86.7–95.8%) for cOCT improvement in diagnostic performance ($P = 0.061$) (Figure 1).

The trade-off between sensitivity and specificity at different thresholds (on the basis of level of confidence) for a positive test result are shown for CE and cOCT (Table 2). When confidence scores 1–4 were considered as test positives and confidence score of 0 as test negative, sensitivity was 97.6% for CE and 95.2% for cOCT ($P = 0.687$). Specificity increased from 47.5% for CE to 76.8% for cOCT ($P < 0.001$). Positive predictive values were 60.9% for CE and 77.5% for cOCT, and negative predictive values were 95.9% and 95.0%, respectively.

When only a confidence score of 4 was considered as test positive and confidence scores 0–3 as test negatives, higher specificity was observed for CE (100%) than for cOCT (93.9%) ($P = 0.0313$). Sensitivity of CE (10.8%) was significantly lower than that of cOCT (59.0%) ($P < 0.001$). The positive predictive values increased to 100% for CE and 89.1% for cOCT, whereas negative predictive value decreased to 57.2% for CE and 73.2% for cOCT.

Table 1. Baseline Characteristics of Patient and Lesion-Based Analysis; For Categorical Variables Percentages (Absolute Numbers) Are Given

Characteristic	Patient-Based	Lesion-Based
Mean age (SD)	66.8 (13.0)	67.4 (13.5)
Sex, n (%)		
Male	93 (51.1)	
Female	83 (45.6)	
Localization, n (%)		
Head/neck	96 (52.7)	123 (49.2)
Trunk	51 (18.0)	72 (28.8)
Extremities	35 (19.2)	55 (22.0)
Number of lesions (%)		
1	134 (73.7)	
2	37 (20.3)	
3	7 (3.8)	
4	2 (1.1)	
6	2 (1.1)	
Histologic diagnosis, n(%)		
BCC	83 (45.6)	116 (46.4)
No BCC	99 (54.4)	134 (53.6)
BCC subtypes, n(%)		
Superficial BCC	26 (31.3)	34 (29.3)
Nodular BCC	36 (43.4)	56 (48.3)
Aggressive BCC	21 (25.3)	26 (22.4)
Other diagnoses (non-BCC), n(%)		
Benign[1]	48 (48.4)	62 (46.3)
SCC	19 (19.2)	23 (17.2)
Actinic keratosis	17 (17.2)	24 (17.9)
Bowen's disease	13 (13.1)	23 (17.2)
Atypical fibroxanthoma	1 (1.0)	1 (0.7)
CD30 proliferation	1 (1.0)	1 (0.7)

Abbreviations: BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

[1]Including: sebaceous gland hyperplasia and/or adenoma, dermatofibroma, folliculitis, dermal nevus, seborrhoic keratosis, scar, pseudolymphoma, interfase dermatitis, benign lichoid keratosis.

Ability to distinguish between subtypes of basal cell carcinoma

Accurate subtyping of BCCs is important to decide whether an excision is indicated (nonsuperficial BCC) or whether the BCC can be treated noninvasively (superficial BCC). There were 83 histologically confirmed BCCs in the database (57 nonsuperficial BCCs and 26 superficial BCCs).

Of the 83 histologically verified BCCs, CE detected 81 BCCs and cOCT identified 79 BCCs. There was overlap in 77 BCCs (54 nonsuperficial BCCs and 23 superficial BCCs), which were used for the paired comparison of subtyping ability of CE and cOCT (Table 3). Sensitivity to detect nodular and/or aggressive BCC was 87.0% for CE and 88.9% for cOCT ($P = 1$). Specificity to detect superficial BCC significantly increased from 47.8% with CE to 78.3% with cOCT ($P = 0.031$)

Optical coherence tomography in conjunction with clinical images diagnosis of basal cell carcinoma made with high confidence (level 4)

In a clinical scenario, high confidence in the presence of BCC according to cOCT diagnosis could lead to a treatment decision without the need for verification of the histopathologic diagnosis by punch biopsy. To evaluate the outcome of this potential scenario, the ability to predict BCC and subtype was evaluated within the group of cases in which BCC was diagnosed by cOCT with a confidence score of 4. Certainty about presence of BCC and subtype according to cOCT was observed in 55 of 182 patients (30%) (Table 4). According to histopathology, 49 of those 55 lesions were BCCs (positive predictive values = 89.1%). The other six diagnoses were one actinic keratosis, one sebaceous gland adenoma, one Bowen's disease, two interface dermatitis, and one benign lichenoid keratosis.

According to histologic subtyping, those 49 BCCs consisted of 15 superficial BCCs and 34 nonsuperficial BCCs. With respect to subtyping, sensitivity to detect nonsuperficial BCCs was 94.1% (32 of 34) for cOCT compared with 91.1% (31 of 34) for CE ($P = 1$). Specificity for cOCT was 86.7% (13

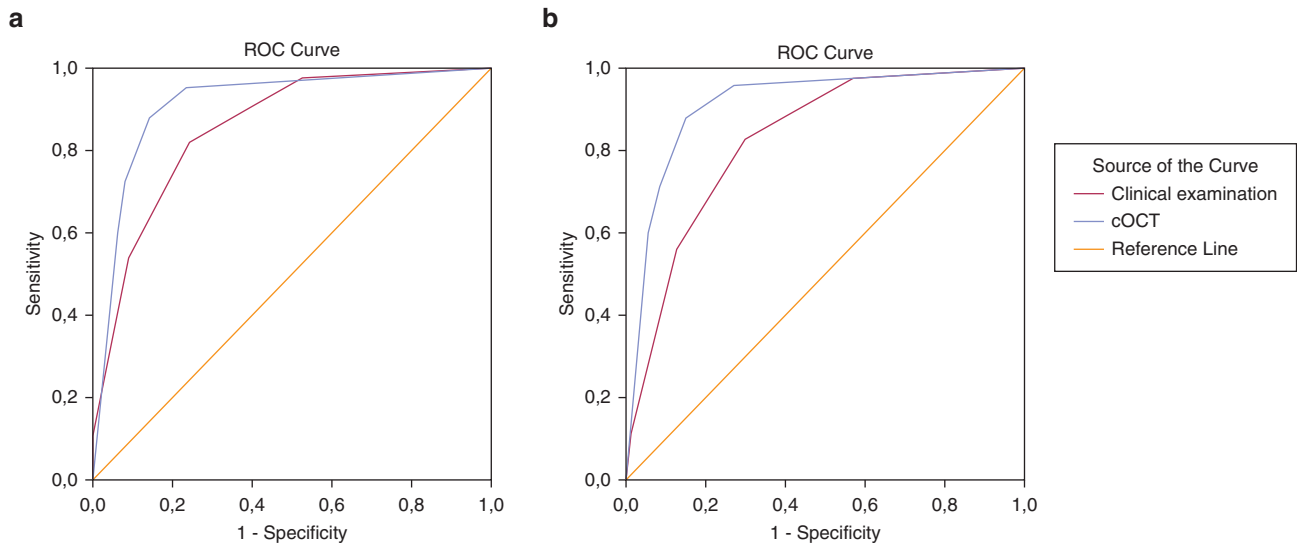

Figure 1. ROC curves for clinical examination and cOCT. cOCT, optical coherence tomography in conjunction with clinical images; ROC, receiver operating characteristic.

of 15) and higher than that for CE at 53.3% (8 of 15) ($P = 0.063$) (Table 3).

Table 4 shows that, in total, 18 BCCs were classified as superficial BCC by cOCT, but five of these lesions were misclassified. Of those, two were nonsuperficial BCC (nodular BCC) and three lesions turned out to be two interface dermatitis and one benign lichenoid keratosis. A total of 37 lesions were classified as nonsuperficial BCC by cOCT. Of those, 32 were indeed nonsuperficial BCC. A total of two lesions were actually superficial BCC and three lesions turned out to be one Bowen's disease, one actinic keratosis, and one sebaceous gland adenoma.

Lesion-based analysis

The 182 patients who were included in this study had a total of 250 lesions. The number of patients with one or more lesions are described in Table 1. The 250 lesions consisted of 116 BCCs and 134 non-BCCs, corresponding to a BCC prevalence of 46%. Of the 116 BCCs, 34 (29.3%) were superficial BCCs, 56 (48.3%) nodular BCCs, and 26 (22.4%) aggressive BCCs. The results from lesion-based analyses are

Table 2. Diagnostic Performance of CE and OCT in cOCT from Patient-Based (182) and Lesion-Based (250) Analyses. Sensitivity and Specificity are Given for Various Cutoff Values of the Confidence Score

	Patient-based CE, % (CI)	Patient-based cOCT, % (CI)	Lesion-based CE, % (CI)	Lesion-based cOCT, % (CI)
Cutoff 1234 versus 0				
Sensitivity	97.6 (90.8–99.6)	95.2 (87.5–98.4)	97.4 (92.1–99.3)	95.7 (89.7–98.4)
Specificity	47.5 (37.4–57.7)	76.8 (67.0–84.4)	43.3 (34.8–52.1)	73.1 (64.7–80.2)
PPV	60.9 (52.0–69.1)	77.5 (67.9–84.9)	59.8 (52.4–66.8)	75.5 (67.6–82.1)
NPV	95.9 (84.7–99.2)	95.0 (87.0–98.4)	95.1 (85.4–98.7)	95.1 (88.5–98.2)
Cutoff 234 versus 01				
Sensitivity	81.9 (71.6–89.2)	88.0 (78.5–93.8)	82.8 (74.4–88.9)	87.9 (80.3–93.0)
Specificity	75.8 (65.9–83.6)	85.9 (77.1–91.8)	70.1 (61.5–77.6)	85.1 (77.6–90.4)
PPV	73.9 (63.5–82.3)	83.9 (74.1–90.6)	70.6 (62.1–77.9)	83.6 (75.6–89.5)
NPV	83.3 (73.7–90.1)	89.5 (81.1–94.6)	82.5 (73.9–88.7)	89.1 (82.0–93.7)
Cutoff 34 versus 012				
Sensitivity	54.2 (43.0–65.1)	72.3 (61.2–81.3)	56.0(4.5–65.1)	70.7 (61.4–78.6)
Specificity	90.9 (83.0–95.5)	91.9 (84.2–96.2)	87.3 (80.1–92.2)	91.8 (85.4–95.6)
PPV	83.3 (70.2–91.6)	88.2 (77.6–94.4)	79.3 (68.6–87.1)	88.2 (79.4–93.7)
NPV	70.3 (61.5–78.0)	79.8 (71.1–86.5)	69.6 (62.0–76.4)	78.3 (70.9–84.3)
Cutoff 4 versus 0123				
Sensitivity	10.8 (5.4–20.1)	59.0 (47.7–69.5)	12.1 (6.9–19.7)	58.6 (49.1–67.6)
Specificity	100 (95.3–100.0)	93.9 (86.8–97.5)	98.5 (94.2–99.7)	94.8 (89.1–97.7)
PPV	100 (62.8–100.0)	89.1 (77.1–95.5)	87.5 (60.4–97.8)	90.7 (81.1–95.8)
NPV	57.2 (49.5–64.6)	73.2 (64.5–80.5)	56.4 (49.8–62.8)	72.6 (65.2–78.9)

Abbreviations: CE, Clinical Examination; CI, confidence interval; cOCT, OCT in conjunction with clinical images; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value.

Table 3. Ability to Distinguish between Superficial and Nonsuperficial BCC of CE and OCT in cOCT

	Patient-based CE, % (CI)	Patient-based cOCT, % (CI)	*P*-value (McNemar test)	Lesion-based CE, % (CI)	Lesion-based cOCT, % (CI)	*P*-value (McNemar test)
All BCCs that were identified both by CE and cOCT; 54 non-sBCC and 23 sBCC						
Sensitivity	87.0 (47/54)	88.9 (48/54)	1.00	85.9 (67/78)	83.3 (65/78)	0.727
Specificity	47.8 (11/23)	78.3 (18/23)	0.031	60.0 (18/30)	80.0 (24/30)	0.031
PPV	79.7 (47/59)	90.6 (48/53)	0.178	84.8 (67/79)	91.5 (65/71)	0.311
NPV	61.1 (11/18)	75.0 (18/24)	0.530	62.1 (18/29)	64.9 (24/37)	0.981
BCCs that were identified by cOCT with high confidence (level 4); 34 non-sBCC and 15 sBCC						
Sensitivity	91.1 (31/34)	94.1 (32/34)	1.00	89.6 (43/48)	85.4 (41/48)	0.625
Specificity	53.3 (8/15)	86.7 (13/15)	0.063	65.0 (13/20)	90.0 (18/20)	0.063
PPV	81.6 (31/38)	94.1 (32/34)	0.209	86.0 (43/50)	95.3 (41/43)	0.243
NPV	72.7 (8/11)	86.7 (13/15)	0.691	72.2 (13/18)	72.0 (18/25)	0.743

Abbreviations: BCC; basal cell carcinoma; CI, confidence interval; CE, clinical examination; cOCT, OCT in conjunction with clinical images; NPV, negative predictive value; OCT, optical coherence tomography; PPV, positive predictive value; sBCC, superficial basal cell carcinoma.

Sensitivity was defined as the proportion of patients with histologically verified nonsuperficial BCC (requiring excision) that were detected. Specificity was defined as the proportion of patients with histologically verified superficial BCC (not requiring excision) that were identified as superficial BCC.

also presented, enabling comparison with the results from patient-based analyses. There were small differences in the estimates for diagnostic parameters, and a statistically significant increase from 82.7% to 91.3% in AUC was observed ($P < 0.001$).

DISCUSSION

This study shows that the use of OCT in conjunction with clinical pictures demonstrates a better ability to differentiate BCC from other diagnoses when compared with CE alone. In both analyses, the AUC indicated better diagnostic performance for cOCT than for CE. When confidence scores 1–4 were considered as test positive (versus score 0 as test negative), addition of cOCT was associated with a significant increase in specificity from 47.5% to 76.8% without compromising sensitivity. Previous studies also found increase in specificity without affecting sensitivity (Cheng et al., 2016; Markowitz et al., 2015; Ulrich et al., 2015).

This study showed that the ability of cOCT to discriminate between superficial and nonsuperficial BCCs (nodular BCC and aggressive BCC) was slightly better compared with that of CE. With cOCT, a larger proportion of histologically verified superficial BCC was detected than with CE, meaning higher specificity of cOCT compared with CE alone. Sensitivity to detect nonsuperficial BCCs (nodular BCC and aggressive BCC) increased only slightly. An explanation for this finding may be that sensitivity of CE alone is already high (87.0%). Nodular BCCs are clinically well recognizable, having characteristic features such as elevation, a pearly translucent margin, and telangiectasia. The typical shiny appearance of a nodular BCC is even better seen when a light beam is moved over the tumor. Owing to the design of the study, the assessors of cOCT had to do with photographs in which elevation and shiny appearance are obviously less clear. Recognition of nodular BCC might improve when cOCT is used directly during CE of a patient.

In this study, we performed both a patient-based and a lesion-based analyses. The patient-based analysis using only one lesion per patient ensures independence of observations and provides information on the proportion of patients who are diagnosed correctly. However, in the patient-based analysis, there is a risk of missing an OCT diagnosis of BCC if a patient with multiple lesions has a BCC or other malignancy in a lesion that is not included for analysis. This occurred in one patient. The lesion-based analysis gives information on the proportion of lesions with a correct diagnosis and is also relevant because generally treatments are chosen per lesion. Treatments of BCC lesions are usually not systemic and the decision to treat one lesion and leave one untreated can be taken at once. Although there were small differences in the estimates of diagnostic parameters, both analyses led to similar conclusions. A significant difference in AUC between cOCT and CE was found in the lesion-based analysis, but significance was not reached in the patient-based analysis owing to a limited power.

Table 4. BCC Diagnosis and Subtyping by cOCT Correlated to Histopathologic Diagnosis for Patient-Based (55) and Lesion-Based (75) Analysis Diagnosed with High Confidence (score 4)

	Histopathology Patient-Based				Histopathology Lesion-Based			
	No BCC	Superficial	Nonsuperficial	Total	No BCC	Superficial	Nonsuperficial	Total
cOCT								
Superficial	3	13	2	18	3	18	7	28
Nonsuperficial	3	2	32	37	4	2	41	47
Total	6	15	34	55	7	20	48	75

Abbreviations: BCC, basal cell carcinoma; cOCT, OCT in conjunction with clinical images; OCT, optical coherence tomography.

The idea has been put forward that noninvasive diagnostic techniques, such as OCT, may make it possible to omit punch biopsy in part of the patients for whom the OCT diagnosis of BCC can be made with high confidence (Cheng et al., 2016; Markowitz et al., 2015). In this way, the delay caused by the necessity for a punch biopsy could be avoided. For this reason, this study evaluated whether the predictive value in case of high confidence in the cOCT diagnoses was high enough to guarantee that the prognosis of patients was not compromised and that over- or undertreatment could be avoided. In this study, high confidence (level 4) in BCC diagnosis with cOCT was observed in 30% (55 of 182) of patients.

Within the subgroup of 55 lesions in which BCC was diagnosed with high confidence by cOCT, six lesions turned out not to be BCC after histologic verification. In one case, Bowen's disease was diagnosed by cOCT as nodular BCC with high certainty (score 4). If treatment would have been started on the basis of the cOCT diagnosis, the treatment would have been surgery, which is an adequate treatment for Bowen's disease. In one patient with two lesions, the second lesion (not included in the patient-based analysis) was a histologically verified squamous cell carcinoma that was diagnosed as nodular BCC by cOCT. Treatment would have been surgery, but misclassification of invasive tumors like squamous cell carcinoma or melanoma as BCC is always undesirable.

For subtyping of BCC, two of the 55 lesions diagnosed as BCC with high confidence were histologically nodular BCC that were misdiagnosed as superficial BCC. Consequently, these lesions would have been treated with noninvasive therapy instead of surgical excision. Treatment of nodular BCC with imiquimod is inferior to surgical excision, but results of the SINS trial showed a 5-year sustained clearance of 81% and recurrences are detected early and can easily be retreated with excision (Williams et al., 2017). Unnecessary surgery could have occurred in the patients with actinic keratosis and sebaceous gland adenoma, both misdiagnosed as nodular BCC. The patients with interface dermatitis and benign lichenoid keratosis that were diagnosed as superficial BCC by cOCT would probably have been overtreated with noninvasive therapy. The risk of over- or undertreatment must be weighed against the advantage of treatment without diagnostic delay and less invasive procedures. More importantly, the scenario described above is a hypothetic scenario, and whether OCT-guided diagnosis and treatment compromised effectiveness in terms of remaining free from recurrences in the long term cannot be concluded from this diagnostic study and needs to be verified in a randomized trial comparing the long-term effect of an OCT-guided strategy with standard care.

Instead of retrospectively looking at the scans and the opportunity to obtain a second scan of a different area within the tumor in case of doubt of the diagnosis, a real-time scanning could benefit the outcome of the OCT-guided strategy. As with all diagnostic procedures, increased training yields better results. In this study, we excluded the first 150 scans for training purposes. Therefore, the diagnostic performance of OCT is likely to improve after more training.

In conclusion, this study shows that the use of cOCT improves ability to distinguish between BCC and other diagnoses in patients with lesions clinically suspected for a non-melanoma skin cancer or premalignancy. Ability to distinguish between BCC subtypes needs further improvement. This may be realized with more training and under optimal conditions using OCT directly during CE of a patient. If treatment would be guided by OCT diagnosis, a punch biopsy could be omitted in about 30% of patients. This strategy harbors a small risk of misclassifications.

METHODS AND MATERIALS

A prospective cohort study was conducted at the Dermatology outpatient clinic of the Maastricht University Medical Center, Maastricht, The Netherlands. Adult patients (18 years or older) receiving a skin biopsy of a lesion clinically suspected for a non-melanoma skin cancer or premalignancy were included in this study. Patients who were incompetent to sign informed consent were excluded.

CE consisted of macroscopic and/or visual examination and dermoscopic evaluation (Heine Delta 20T) by the treating physicians. The level of confidence in the diagnosis was documented using a 5-point Likert-scale ranging from 0 to 4 by the treating physician (Figure 2). If there was any suspicion of BCC on the basis of clinical characteristics (such as shiny border, telangiectasia, ulceration) and dermoscopic findings (such as telangiectasia or ovoid nests), the most likely BCC subtype (superficial, nodular, or aggressive) was recorded by the physician. The physician marked the biopsy area of the clinically most aggressive part and a photograph was taken by a medical photographer (Nikon D750). A dermoscopic image was only taken if indicated by the physician. In the same patient consultation, the marked biopsy area was scanned with OCT without any preparations of the skin in advance (Vivosight Multi-beam Swept-Source Frequency Domain OCT, Michelson Diagnostics, Maidstone, Kent, United Kingdom; specifications: class 1 eye safe, resolution <7.5 μm lateral, <5 μm axial, depth of focus = 1.0 mm, scan area = 6 × 6 mm). During the same consultation and following the OCT scan, a 3 mm punch biopsy was taken according to regular care. The histopathologic outcome served as the gold standard and was diagnosed by independent specialized dermato-pathologist with over 10 years of experience, blinded to the OCT images. BCC subtypes were classified as either superficial, nodular, or aggressive BCC. In case of mixed subtypes, the most aggressive subtype was used for analysis.

OCT images were coded and saved anonymously. These OCT images in conjunction with clinical photographs (cOCT) were assessed by two researchers who had received training and had previous experience with OCT. Diagnosis was based on the criteria for OCT

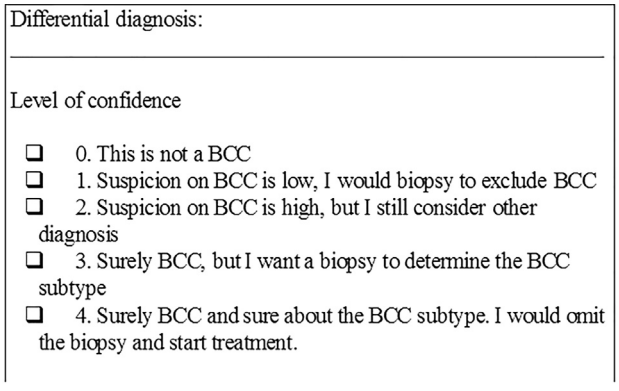

Figure 2. Classification of diagnosis according to level of confidence in BCC diagnosis and BCC subtype. BCC, basal cell carcinoma; DD, differential diagnosis.

assessment, as previously described (Hussain et al., 2015). The two researchers documented the level of confidence in the ultimate diagnosis that was reached by consensus using the 5-point Likert-scale. When BCC was suspected, BCC subtype was also recorded (Figure 2). The assessors were blinded for the results of histopathologic examination. This study was approved by the local independent Ethics Committee. All patients provided written informed consent.

Statistical analysis

This study was based on data from 182 patients with a total of 250 lesions. The data were part of a dataset of 400 lesions in 289 consecutive patients between February 2017 and May 2017. The first 150 lesions were used for training purposes. Before this study, it was assumed that the prevalence of BCC in our study population of patients suspected for non-melanoma skin cancer or premalignancy was about 45% (on the basis of retrospective unpublished data of our department). The goal was to evaluate whether the use of cOCT will result in an increase of specificity when compared with CE alone at similar sensitivity. On the basis of the literature, sensitivity and specificity of CE were estimated at 95% and 45%, respectively (Markowitz et al., 2015, Ulrich et al., 2015). Thus, 100 patients without BCC (55% of 182) were expected to be available for evaluation of specificity. This number enabled detection of an increase of specificity by 20% or more (from 45% to 65%) with a power of 80% (two-sided alpha = 5%).

The primary analysis was performed on the level of patients, where only one lesion per patient was included to ensure independence of observations. A secondary analysis was performed on the level of lesions. The diagnostic performance of CE alone and OCT images in cOCT was expressed by sensitivity, specificity, positive predictive value, negative predictive value, and AUC with corresponding 95% confidence intervals.

Receiver operating characteristic curves were constructed, where each point on the receiver operating characteristic curve represented a sensitivity and specificity pair corresponding to different thresholds for a positive test result. Receiver operating characteristic curves visualized the trade-off between sensitivity and specificity and the AUC was used as a measure of global diagnostic performance (Obuchowski, 2003).

With respect to the ability of cOCT to distinguish between BCC subtypes, we focused on the ability to discriminate between superficial BCC and nodular and/or aggressive BCC. This distinction was relevant to decide whether excision was required or not. For BCC subtyping, sensitivity was defined as the proportion of patients with histologically verified nonsuperficial BCC (requiring excision) that were detected. Specificity was defined as the proportion of patients with histologically verified superficial BCC (not requiring excision) that were identified as superficial BCC.

Differences in diagnostic performance parameters between CE alone and cOCT were tested for statistical significance using the McNemar test for paired proportions. For the paired comparison between the AUC of CE and cOCT, an algorithm developed by DeLong et al. was used (DeLong et al., 1988).

SPSS (version 23) and STATA (version 13.1, StataCorp LLC, College Station, TX) were used for statistical analyses. Two-sided *P*-values of 5% were considered to indicate statistical significance.

Data availability statement

Data sets related to this article can be found at https://dataverse.nl/dataset.xhtml?persistentId=hdl:10411/XOULRC, hosted at Datahubmaastricht (OCT in BCC diagnosis).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

The authors thank the Maurits en Anna Stichting for the funding received to purchase the OCT.

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