SHORT COMMUNICATION

Accuracy of Optical Coherence Tomography for Subtyping Basal Cell Carcinoma: Using Histopathology of Biopsy and Entire Lesion as Reference Standard

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The increasing incidence of basal cell carcinoma (BCC) combined with the disadvantages of invasive diagnostic punch biopsy increase the need for non-invasive diagnostic alternatives, such as optical coherence tomography (OCT) (1, 2). OCT is a non-invasive diagnostic tool that can be used to detect and subtype BCC (**Fig. 1**) (3). OCT may replace punch biopsy (gold standard) only if OCT assessors can detect and subtype BCC with a high level of confidence (2). However, Sinx et al. (2) reported that subtyping BCCs using OCT remains challenging after evaluating the diagnostic accuracy of BCC subtyping using OCT. They used histopathological examination of a punch biopsy as reference standard. However, a single OCT scan always visualizes an area with a diameter of 6 mm. Hence, the question arises as to whether part of the tumor detected on OCT may be missed by punch biopsy, and thus may be misclassified as false-positive if this part contains other histopathological subtypes (4–6). This could lead to biased estimation of the diagnostic accuracy of OCT.

In this study, we aimed to assess the diagnostic accuracy for BCC subtyping on OCT when using two different standards of reference. Diagnostic accuracy using histopathology of a diagnostic punch biopsy as reference standard was compared to that with use of histopathology of the subsequent therapeutic excision specimen.

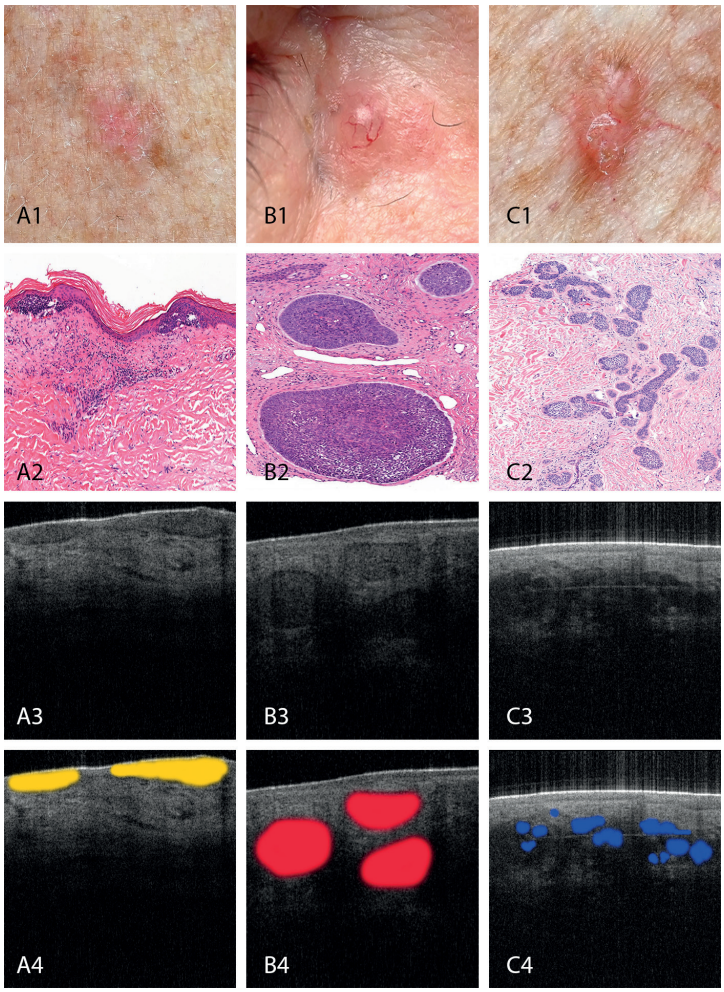

Fig. 1. Clinical (1), histopathological (2), optical coherence tomography (OCT) (3) and highlighted OCT presentation (4) of: (A) superficial, (B) nodular and (C) infiltrative basal cell carcinoma (BCC). All histopathological images have been stained by hematoxylin and eosin and are magnified 10x.

MATERIALS AND METHODS

Included were consecutive patients (age 18 years or older) undergoing a punch biopsy and subsequent excision for BCC. The patient's treating physician marked the clinically most aggressive part of the tumour for punch biopsy. Subsequently, the lesion was scanned with OCT (Vivosight, Michelson Diagnostics, Kent, UK; resolution <7.5 mm lateral, <5 mm axial; depth of focus 1.0 mm; scan area 6x6 mm²) by one expert OCT assessor. The BCC subtype was based on established morphological BCC subtype features (7, 8).

Histopathological examination of punch biopsy and excision specimen was performed by dermatopathologists blinded to the OCT scan and OCT diagnosis made. Histopathological BCC subtypes were classified as superficial, nodular or infiltrative (9). Mixed histopathological subtypes were classified as the most aggressive subtype present (superficial BCC (sBCC) least aggressive, infiltrative BCC (iBCC) most aggressive).

The diagnostic performance of OCT in BCC subtyping was established using 2 different reference standards: (*i*) histopathology of the diagnostic punch biopsy (*ii*) histopathology of the subsequent therapeutic excision. If no residual tumour was found in the excision specimen, or if the biopsy revealed a more aggressive subtype than found in the excision specimen, we used the histopathology of the punch biopsy as the reference standard, as biopsy could have removed the most aggressive subtype. In this case biopsy is the most representative to determine the subtype.

The diagnostic performance of OCT for BCC subtyping was evaluated in cases with a high confidence BCC diagnosis. The OCT assessor was blinded to clinical and visual information about the lesion and histopathology. The diagnostic performance of OCT was expressed as

sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR). Differences in diagnostic parameters were tested for statistical significance using a Chi square test for unpaired proportions. A p-value ≤0.05 was considered to indicate statistical significance.

RESULTS

The cohort comprised 131 patients with histopathologically verified BCCs (mean age 70 years, range 28–95 years). Of those, 13 cases (9.9%) were sBCC, 81 (61.8%) were nBCC and 37 (28.2%) were iBCC. In 110 cases (82.7%) the OCT assessor could determine a BCC subtype with high confidence and these cases were used for further analyses.

Among the 110 included cases, no remaining tumour was found in 17 excision specimens (15.5%) in which the subtype on the punch biopsy was considered the true subtype. By using the excision specimen as reference standard instead of the punch biopsy, 7 (6.4%) BCC subtypes were classified differently. Four BCC subtypes classified as sBCCs on punch biopsy were classified as 3 nBCCs and 1 iBCC on excision, whereas 3 BCC subtypes classified as nBCCs on punch biopsy were classified as iBCCs on excision (**Table I**). The ability to discriminate each BCC subtype from the other 2 subtypes on OCT scans was evaluated (**Table II**). Slight, but non-significant, reductions were observed in almost all diagnostic parameters, including sensitivity and specificity, when using excision specimen as the reference standard instead of punch biopsy.

DISCUSSION

The use of the excision specimen as reference standard resulted in the identification of 3 extra histopathological nBCCs and 4 extra histopathological iBCCs compared to punch biopsy. OCT (the diagnostic test under study) classified only part of these lesions correctly, and this resulted in an increased number of false-negative and false-positive results on OCT and a net decrease in sensitivity and specificity of OCT for discrimination between subtypes.

There are several explanations why more aggressive BCC subtypes are not always recognized on OCT. One case had an infiltrative subtype, but was classified as sBCC on OCT. The superficial component was clearly visible, but squamae caused shading making deeper layers of the scan difficult to analyse. Furthermore, aggressive subtypes tend to grow deeper into the dermis (10), but the resolution of OCT decreases as the penetration depth increases (11). This may also explain why the other 3 iBCCs were misclassified as nBCC on OCT.

Three cases misclassified on OCT and punch biopsy had both superficial and nodular subtypes. On OCT, the superficial component was evident. The nodular component was less evident, as the demarcation between epidermis and ovoid nests, which is an important differentiator between sBCC and nBCC, was unclear. The nodular component was also missed on punch biopsy, which could be the result of sampling error (12). The marked punch biopsy site and subsequent OCT probe placement is important, particularly in larger lesions, as the most aggressive subtype may be present outside the biopsied area. Hence, it is advisable to scan the entire lesion, which is quick and may reveal additional information on the BCC subtype.

In this study population with a low prevalence of sBCC, negative predictive value is highest when OCT is used for discrimination between sBCC and nBCC/iBCC; hence, in this population OCT has high ability to exclude sBCC in case of a diagnosis of nBCC or iBCC. The ability to exclude nBCC or iBCC in case of OCT diagnosis of another BCC subtype is lower and in this respect, there is need for improvement. Misclassification of sBCC as a more aggressive BCC will deprive patients of the choice of non-invasive treatment options. The poor ability of OCT to exclude nBCC or iBCC is of greater clinical concern, because misclassification of nBCCs and iBCCs may lead to insufficient treatment.

In conclusion, the results do not confirm the hypothesis that with respect to discrimination between BCC sub-

Table I. Basal cell carcinoma (BCC) subtyping by punch biopsy and excision specimen as reference standard

	BCC subtype on excision specimen		
BCC subtype on punch biopsy	sBCC	nBCC	iBCC
sBCC	13	3	1
nBCC	0	67	3
iBCC	0	0	23
Total	13	70	27

iBCC: infiltrative basal cell carcinoma; nBCC: nodular basal cell carcinoma; sBCC: superficial basal cell carcinoma.

Table II. Diagnostic performance of optical coherence tomography (OCT) with excision specimen or punch biopsy as reference standard

	OCT with excision specimen as reference standard (n = 110) % (x/n) (95%CI)*	OCT with punch biopsy as reference standard (n = 110) % (x/n) (95% CI)*	p-value
sBCC vs nBCC/iBCC			
Sensitivity	61.5 (8/13) (35.6–81.1)	64.7 (11/17) (44.2–74.3)	0.866
Specificity	94.8 (92/97) (91.4–97.5)	97.8 (91/93) (94.1–99.6)	0.306
PPV	61.5 (8/13) (35.6–81.1)	84.6 (11/13) (57.8–97.1)	0.226
NPV	94.8 (92/97) (91.4–97.5)	93.8 (91/97) (90.2–95.5)	0.756
DOR (95%CI)	29.4 (5.9–165.2)	83.4 (12.7–721.3)	
nBCC vs sBCC/iBCC			
Sensitivity	88.6 (62/70) (81.6–94.0)	90.0 (63/70) (83.1–95.1)	0.785
Specificity	50.0 (20/40) (37.8–59.5)	52.5 (21/40) (40.4–61.4)	0.823
PPV	75.6 (62/82) (69.7–80.2)	76.8 (63/82) (70.9–81.2)	0.855
NPV	71.4 (20/28) (54.0–84.9)	75.0 (21/28) (57.8–87.7)	0.763
DOR (95%CI)	7.8 (2.7–22.9)	9.9 (3.3–30.7)	
iBCC vs nBCC/iBCC			
Sensitivity	33.3 (9/27) (19.3–45.2)	39.1 (9/23) (22.8–52.9)	0.670
Specificity	92.8 (77/83) (88.2–96.6)	93.1 (81/87) (88.8–96.7)	0.933
PPV	60.0 (9/15) (34.7–81.4)	60.0 (9/15) (35.0–81.1)	>0.999
NPV	81.1 (77/95) (77.1–84.4)	85.3 (81/95) (81.3–88.6)	0.438
DOR (95%CI)	6.4 (1.8–23.8)	8.7 (2.3–33.4)	

95% CI: 95% confidence interval; DOR: diagnostic odds ratio; iBCC: infiltrative basal cell carcinoma; nBCC: nodular basal cell carcinoma; NPV: negative predictive value; PPV: positive predictive value; sBCC: superficial basal cell carcinoma.

types, the diagnostic accuracy of OCT becomes higher when using the excision specimen as reference standard instead of punch biopsy. The diagnostic parameters for OCT were even slightly lower. However, the results of this study show that bias may be limited in diagnostic studies, wherein excision specimens are not available for all patients and the use of punch biopsy as the reference standard is the only option.

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