

The utility of optical coherence tomography for diagnosis of basal cell carcinoma: a quantitative review*

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Summary

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Background Optical coherence tomography (OCT) is a noninvasive near-infrared light imaging technology that can be utilized to diagnose basal cell carcinomas (BCCs) based on specific morphological features.

Objectives To conduct a quantitative review using tumour-level data from published studies to assess: (i) the in vivo diagnostic accuracy of different OCT systems; (ii) correlation between OCT features and histopathological diagnosis; and (iii) factors that impact the accuracy of tumour depth estimation.

Methods Primary tumour-level data were extracted from published studies on the use of time-domain (TD-OCT), frequency-domain (FD-OCT) and high-definition (HD-OCT) systems for diagnosis of BCCs. Quality assessment was performed using the Newcastle–Ottawa Scale and the Cochrane Risk of Bias Tool. Sensitivity and specificity for diagnosis of BCC, prevalence of morphological features and correlation of tumour depth between OCT and histopathology were analysed.

Results In total, 901 BCCs from 31 studies were included. The sensitivity and specificity were 89.3% and 60.3% overall, and were highest for FD-OCT (93.7% and 61.4%, respectively). The most prevalent morphological features were lobular pattern (80.2%, 315 of 393 tumours) and hyper-reflective peritumoral stroma (51.7%, 203 of 393). Concordance between OCT and histopathological tumour depth categories was moderate (Pearson coefficient 0.48); it was highest for tumours < 1 mm and those on the extremities. The overall bias was 0.075 mm with an agreement range from –0.88 to 1.03 mm. HD-OCT and FD-OCT were superior to TD-OCT at identifying morphological features, but not at tumour depth estimation.

Conclusions OCT is a viable tool for in vivo diagnosis of BCCs. FD-OCT and HD-OCT outperformed TD-OCT in diagnostic accuracy and detection of morphological features, but not tumour depth estimation.

What's already known about this topic?

- Optical coherence tomography (OCT) is a noninvasive imaging modality that can be used to diagnose basal cell carcinoma (BCC).
- Morphological features found on OCT images correlate with specific histopathological findings.
- OCT can also detect subclinical extension of tumours and improve preoperative delineation of surgical margins.

What does this study add?

- This study analysed tumour-level data from 31 published studies encompassing 901 BCCs.
- We calculated the diagnostic sensitivity and specificity of different OCT systems, determined the degree of correlation between OCT morphological features and BCC diagnosis and analysed tumour and machine factors that affect OCT estimation of tumour depth.

Basal cell carcinoma (BCC) is the most common type of skin cancer. Its incidence in Europe has increased at an alarming rate of 5.5% per year over the past four decades.¹ In the U.K., the incidence of BCC has risen at a rate six times higher than in the rest of Europe.¹ A similar trend is observed in the U.S.A. Studies have estimated an increase ranging from 2% to 11% per year in the incidence of cases of BCC, with approximately 200–400 new cases per 100 000 persons each year.^{1,2} Diagnosis of BCC typically requires a skin biopsy and histopathological exam. More recently, noninvasive imaging modalities such as dermoscopy, confocal microscopy and optical coherence tomography (OCT)³ have been used to diagnose BCC.

OCT is an imaging technology analogous to ultrasonography, except it utilizes near-infrared light rather than acoustic waves to generate real-time, noninvasive cross-sectional images of biological tissues.^{3,4} OCT was introduced into the field of dermatology in 1997 when Welzel *et al.* used the technology to image human skin.⁵ It has since shown promising results in several studies as a diagnostic tool.^{3,6–15} By measuring the reflected or backscattered light from a sample of skin tissue through a process known as interferometry, it is possible to visualize structures such as the epidermis, dermoepidermal junction (DEJ), dermis, hair follicles, sweat glands and blood vessels.^{5,16,17} It is also possible to visualize morphological features of pathological structures within the skin such as a BCC lesion (Fig. 1).

Early OCT machines, known as time-domain (TD)-OCT, provide penetration depths of up to 2 mm at resolutions of approximately 10–15 μm .¹⁸ At greater depths, resolution is sacrificed, resulting in poorer differentiation of microstructures and cellular details.¹⁷ Conversely, improving the resolution of cellular details will result in a more limited penetration depth.^{3,17} Recent advances in OCT technology have made it possible to overcome some of the limitations of TD-OCT. High-definition (HD)-OCT offers significantly improved resolutions of 1–3 μm while sacrificing only some penetration depth (570–750 μm).^{19,20} Frequency- or Fourier-domain (FD)-OCT systems seek to combine the best aspects of TD-OCT and HD-OCT, offering a higher resolution (7.5 μm) than TD-OCT and higher penetration depths (1.2–1.8 mm) than HD-OCT.²⁰ The newer types of OCT machines enable

better visualization of skin structures and more accurate characterization of pathological features at greater depths and higher resolutions.^{3,20,21}

Prior literature reviews have highlighted the technological principles of OCT and its utility in diagnosing BCCs.^{22–25} However, these reviews provide mainly qualitative summaries of published results. There has been no quantitative analysis using tumour data to determine the overall sensitivity and specificity of OCT for diagnosing BCCs or to analyse tumour and machine factors that may influence the diagnostic accuracy of OCT. Therefore, we conducted a quantitative review of primary data to assess the following: (i) the sensitivity and specificity of different OCT systems for *in vivo* diagnosis of BCC; (ii) correlation between OCT features and histopathological findings; and (iii) the impact of tumour and machine factors on tumour depth estimation by OCT.

Materials and methods

Search methodology

A search of the MEDLINE and Embase databases was conducted using (i) MeSH terms: 'Coherence, Optical Tomography[mh] AND (Carcinoma, Basal Cell[mh] OR Carcinoma, Squamous Cell[mh])' and (ii) keywords in the manuscript: basal cell carcinoma, BCC, squamous cell carcinoma, SCC, non-melanoma skin cancer, optical coherence tomography, OCT, dermatology, skin.

Study inclusion and exclusion criteria

Clinical studies on the use of OCT on *in vivo* human skin to aid in the diagnosis of BCC or squamous cell carcinoma (SCC) were screened by N.R. based on the following inclusion criteria: publication in the English language, BCC diagnosis confirmed by gold-standard histopathology, available primary data on OCT morphological features, histopathological findings, and depth for individual tumours. Studies on the utility of OCT in detecting BCC local recurrences, and those that investigated system technical parameters on OCT image quality without data on specific morphological features were excluded.

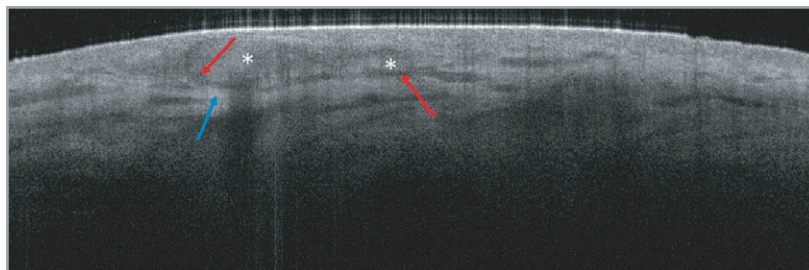


Fig 1. An optical coherence tomography image of a BCC lesion with several visible morphological features: lobular structures of the tumour (asterisks); a dark ring-like pattern surrounding the tumour representing peripheral rimming (red arrows); and hyper-reflective stroma below the lesion (blue arrow).

There were no exclusions based on patient age, sex or ethnicity, or the type of OCT system studied.

Data inclusion and exclusion criteria

Data on SCC and premalignant or in situ lesions such as actinic keratoses and Bowen disease were excluded. Studies using the same patient groups had their data combined during the data collection process.^{12,13} If data from multiple interpreters were provided, the results from the most experienced interpreter were selected. Tumour depth values were estimated based on the provided plot for one study.²⁶ For articles containing primary data related to diagnostic accuracy, non-BCC tumours were included in the dataset for calculation of sensitivity and specificity.

Assessment of risk of bias

The Newcastle–Ottawa Scale (NOS) was used to assess the quality and risk of bias for cohort and case–control studies and their subset of tumours included in this review.²⁷ The NOS assesses three domains including selection of patients, comparability of patient groups and reporting of outcomes.²⁷ The NOS uses a star rating system for each domain. A maximum of four stars is given for the patient selection category, two for comparability and three for the exposure or outcome. A higher rating corresponds to a lower risk of bias.

Given the lack of validated tools for quality assessment of noncomparative studies, we employed a previously used, modified NOS for evaluation of case series and case reports included in the review.^{28–32} In this adapted version, items associated with comparability and adjustment were removed, while those focusing on patient selection, case representativeness and reporting of exposure and outcome were retained. The modified NOS contains five criteria, each of which was given a star if met (Table S1; see Supporting Information). Meeting all five criteria resulted in a rating of 5 stars.

For the single randomized controlled trial study, quality was assessed using the Cochrane Risk of Bias Tool,³³ which focuses on seven domains: random sequence generation, allocation concealment, selective reporting, blinding of participants, blinding of assessment, incomplete outcome data and other bias. A trial with at least one domain considered to have a high risk or unclear risk of bias was designated as having an overall high risk of bias.

Data analysis

Primary data pertaining to OCT and histopathological diagnosis, BCC morphological features and/or tumour depth were collected on individual tumours from each study. Statistical analyses were performed on the combined tumour data using SAS software v9.3 (SAS Institute Inc., Cary, NC, U.S.A.) and R version 3.4 (https://www.r-project.org). Average sensitivity, specificity and predictive values were calculated by comparing OCT and histopathological diagnoses for each tumour. Frequency tabulation was used to analyse the prevalence of BCC morphological features on OCT.

Bland–Altman analysis was performed on aggregate tumour depth data to assess the agreement levels between OCT depth and histopathological depth. Concordance and Pearson's correlation coefficients were calculated between OCT depth and histopathological depth. Concordance was defined as the difference between the OCT findings and the histopathological results relative to the histopathological results. The agreement levels were further assessed based on device types and features, as well as the histopathological depth and anatomical site of the tumours.

Results

Our search yielded 345 studies, of which 149 were unique, with 134 results from MEDLINE and 15 from Embase (Fig. 2). We had intended to perform a review on the utility of OCT in the diagnosis of BCC and SCC; however, our search yielded limited tumour-level data on SCC. We therefore focused the analysis on BCC. Of the 149 unique studies, 118 were excluded: 104 after review of abstracts and 14 after review of manuscripts. Notable reasons for exclusion include the use of OCT on areas other than skin (41 studies); data on individual Mohs sections, from which tumour-level data were unavailable (four studies); focus on nonmorphological parameters (five studies) and use of OCT for monitoring or detecting tumour recurrence (nine studies).

There were 31 studies published between 2003 and 2017, with 901 BCCs (Table 1 and Table S2; see Supporting Information). The majority of studies (17 of 31) were prospective cohort studies, in which patients with lesions suspicious for BCCs were imaged prior to skin biopsies for histopathological confirmation of diagnosis. The second most common design was retrospective case series (nine of 31), in which the OCT images of patients with histopathologically confirmed BCC were analysed. The number of BCCs in each study ranged from one (case report) to 141. The most common cause of tumour exclusion within the included studies was lack of primary data for individual tumours. Twenty-five studies investigated correlation between OCT morphological features and histopathological findings. Eight studies assessed the diagnostic accuracy of OCT against the histopathological gold standard. Six studies analysed correlation in tumour depth assessment by OCT vs. histopathology.

Most studies (17 of 31) utilized FD-OCT, which was used to image 63% of all BCCs in our review cohort. Four studies utilized HD-OCT, providing data for 13% of tumours. Studies published after 2010 using new FD-OCT and HD-OCT technology had, on average, larger sample sizes (37 ± 38.5 , range 1–141) than those published during 2003–2010 using TD-OCT (22 ± 21.2 , range 2–64). Tumour depth data were available from six studies for only 10% (93 of 901) of tumours. In contrast, 64% of BCCs (579 of 901, from 27 studies) had data on OCT morphological features. Assessments of study quality using the NOS and Cochrane Risk of Bias Tool are detailed in Table S2 (see Supporting

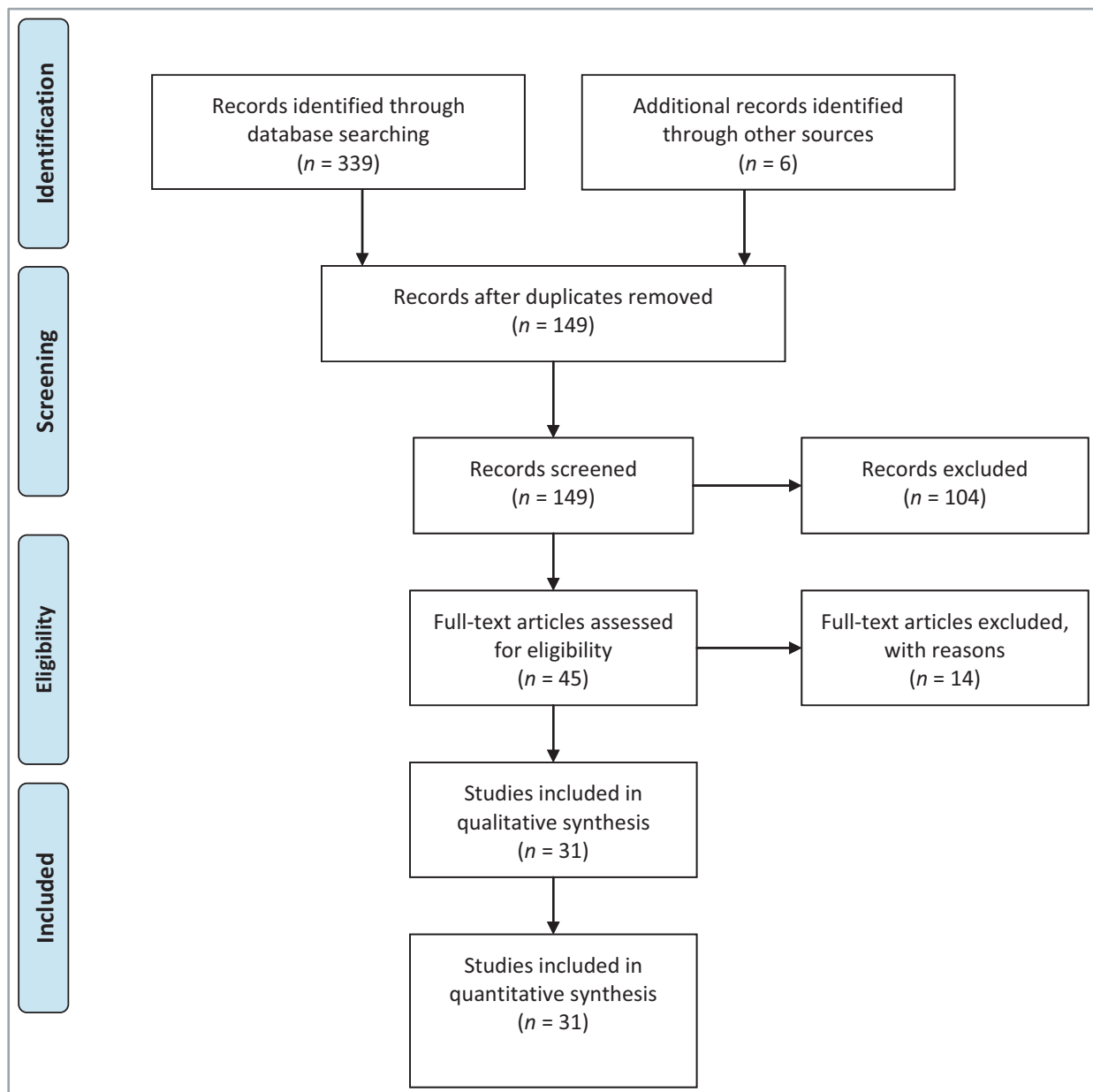


Fig 2. PRISMA flowchart.

Information). The majority of the studies were of high quality and had low risk of bias, with no more than one star missing. The most common source of bias was a lack of representativeness of the cases or cohorts, resulting in a potential selection bias.

Diagnostic accuracy of optical coherence tomography

Parameters of the diagnostic accuracy of OCT, such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated based on the primary data from eight studies, encompassing 477 BCCs (Table 2 and Fig. S1; see Supporting Information). HD-OCT was not used for any of these tumours. FD-OCT outperformed TD-OCT on

all four parameters of diagnostic accuracy, with significantly higher sensitivity (93.7% vs. 77.3%) and correspondingly higher NPV (84.6% vs. 61.3%). Differences in specificities and PPVs were smaller: 3.9% and 6.7%, respectively. Diagnostic accuracy parameters for the cohort were skewed towards those for FD-OCT, as the majority of tumours (73%, 349 of 477) were imaged with FD-OCT.

Prevalence of optical coherence tomography morphological features

The two most prevalent OCT morphological features were lobular pattern and hyper-reflective peritumoral stroma, present in 80.2% (315 of 393) and 51.7% (203 of 393) of tumours,

respectively (Table 3). All morphological features except for hyperkeratosis were more frequently observed in tumours imaged with HD-OCT than with TD-OCT, with the prevalence ranging from 1% to 64% for TD-OCT vs. 18% to 93% for HD-OCT. FD-OCT showed more modest improvements over TD-OCT and revealed a lower prevalence of dilated blood vessels (9% vs. 32%) and hyperkeratosis (17% vs. 42%). The greatest improvement was seen in detecting hyper-reflective peritumoral stroma, noted in only 11% of tumours imaged with TD-OCT but 77% and 52% of tumours imaged with HD-OCT and FD-OCT, respectively. HD-OCT was superior to FD-OCT in detection of all morphological features except for peripheral rimming and disruption of the DEJ (Table 3).

Assessment of tumour depth

Tumour depth category concordance between OCT and histopathological exams, defined as the case when both measured depths were in the same depth category, was 47% for all tumours, 59% for tumours thinner than 1 mm, and only 7.7% for tumours thicker than 1.5 mm (Table 4). Correlation in tumour depth category was moderate overall (Pearson coefficient 0.48). When tumour depth was analysed as a continuous rather than a categorical variable, the percentage discrepancy between OCT and histopathological depth averaged 13.6%. OCT underestimated depth for tumours thicker than 1.5 mm by 40.3% and overestimated depth for tumours thinner than 0.5 mm by 65%. The percentage discrepancy was lowest for tumours on the extremities (1.3%) and highest for those on the head and neck (27.3%). TD-OCT

overestimated tumour depth (average discrepancy 35.7%), while FD-OCT underestimated tumour depth (average discrepancy -20.5%). However, both had moderate correlation to the actual depth (Pearson coefficients 0.64 and 0.51, respectively).

The Bland-Altman method was used to compare OCT and histopathological tumour depth measurements as a function of tumour depth (Fig. 3), yielding a bias of 0.075 mm, with the 95% limits of agreement ranging from -0.88 mm to 1.03 mm. Variability was found to increase with tumour thickness, particularly for tumours > 1 mm.

Discussion

Since its introduction to the field of dermatology in 1997,⁵ OCT technology has significantly improved and enabled better visualization of skin features at greater depths. OCT is now a viable noninvasive method to diagnose BCCs. Our analysis of 477 BCCs from eight studies showed that the overall sensitivity and specificity were 89.3% and 60.3%, respectively. Previous studies reported ranges of 79–94% for sensitivity and 85–96% for specificity. Additionally, a review of 22 studies with 556 BCCs conducted by Cheng and Guitera⁷ concluded that OCT offered high sensitivity and specificity for the diagnosis of BCCs. Our overall specificity was lower due to the higher false-positive rates for both TD-OCT and FD-OCT in this aggregated cohort.

The newer FD-OCT has superior diagnostic accuracy than TD-OCT, with an impressive 93.7% sensitivity and 84.6% NPV. We attribute the superior diagnostic capability of FD-OCT to better resolution and higher depth penetration over TD-OCT. Improvement in these technical parameters allowed better detection of the morphological features of BCC. We were unable to obtain primary data on the diagnostic accuracy of HD-OCT. However, we would expect it to perform similarly to FD-OCT given its high operating resolution.

Table 1 Availability of tumour-level data based on optical coherence tomography (OCT) type and outcome of interest

	No. of studies	No. of tumours	Proportion of total tumours
OCT device type			
Conventional	10	213	24%
High definition	4	118	13%
Fourier domain	17	570	63%
OCT features			
Morphology	27	579	64%
OCT depth	6	93	10%
Diagnostic accuracy	8	477	53%

Table 2 Diagnostic accuracy of optical coherence tomography (OCT) systems (n = 477)

	Sensitivity	Specificity	PPV	NPV
Overall	89.3%	60.3%	79.5%	76.6%
OCT device type				
Conventional	77.3%	57.5%	74.4%	61.3%
Fourier domain	93.7%	61.4%	81.1%	84.6%

PPV, positive predictive value; NPV, negative predictive value.

Table 3 Prevalence of basal cell carcinoma morphological features on optical coherence tomography (OCT) (n = 393)

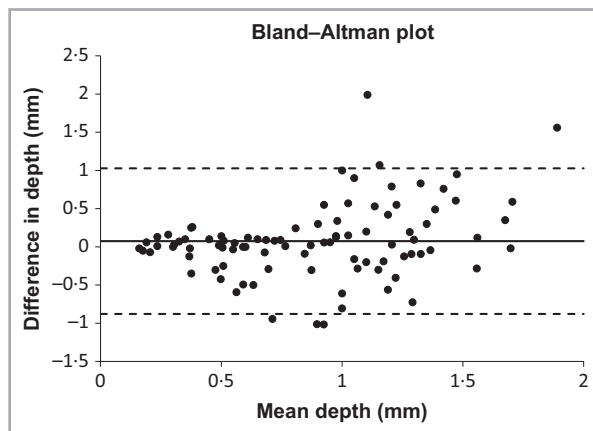
Feature	Overall	Conventional OCT	HD-OCT	FD-OCT
Lobular pattern/hyporeflexive nodules	80%	64%	93%	78%
Hyper-reflective peritumoral stroma	52%	11%	77%	52%
Peripheral rimming	44%	3%	47%	58%
Disruption of dermoepidermal junction	33%	1%	33%	45%
Dilated blood vessels	24%	32%	45%	9%
Hyperkeratosis	22%	42%	18%	17%

HD, high definition; FD, Fourier domain.

Table 4 Tumour depth concordance between optical coherence tomography (OCT) and histopathological exam (n = 93)

	N	Depth category concordance ^a	Discrepancy in depth measurement ^b	PCC (depth category) ^c	PCC (depth) ^d
Overall	93	47.3%	13.6%	0.48	0.51
Histopathological depth of tumour (mm)					
0–0.5	27	59.3%	65.3%	0.48	0.21
> 0.5, ≤ 1	29	58.6%	13.0%	0.48	0.62
> 1, ≤ 1.5	24	41.7%	–15.5%	0.48	–0.07
> 1.5	13	7.7%	–40.3%	0.48	–0.16
Anatomical site					
Head and neck	18	38.9%	–27.3%	0.54	0.45
Trunk	6	66.7%	–23.1%	0.77	0.61
Extremities	6	66.7%	–1.3%	0.89	0.93
OCT device type					
Conventional	56	51.8%	35.7%	0.60	0.64
Fourier domain	37	43.2%	–20.5%	0.51	0.51

PCC, Pearson correlation coefficient. ^aDefined as OCT calculated depth and histopathological depth in the same depth category. ^bDefined as the percentage error between OCT calculated depth and histopathological depth. ^cCorrelation between OCT calculated depth and histopathological depth categories. ^dCorrelation between OCT calculated depth and histopathological depth.

**Fig 3.** Bland–Altman plot comparing tumour depth measured by optical coherence tomography with histopathological depth for 93 paired measurements.

Many of the histological features of BCC have correlates that are commonly found with OCT. Commonly noted features include lobulated nodules, epidermal disarray, peripheral rimming, refractile stroma and dilated blood vessels.^{8,34–36} These features can serve as OCT diagnostic criteria for BCC. Analysis of 393 BCC tumours showed that the most common morphological feature of BCC for all three OCT systems, detected in 80% of all tumours, was lobular pattern with hyporeflective nodules, representing tumour nests. Hyper-reflective peritumoral stroma and peripheral rimming were present in over half of tumours imaged with HD-OCT and FD-OCT. The former has been correlated with highly fibrous stroma surrounding the tumour on histopathology.³⁴ The latter, visualized as a dark band surrounding the tumour nodules on OCT, is

hypothesized to be peritumoral mucin deposition.^{8,21,35} Dilated blood vessels and hyperkeratosis were more commonly detected with TD-OCT, although they were still present in only 30–40% of tumours. HD-OCT outperformed TD-OCT and FD-OCT in detecting morphological features due to its higher resolution, which enables better delineation of structural features. FD-OCT, which trades some resolution for increased depth penetration, trailed HD-OCT in detection of most structural features but proved its depth superiority with better visualization of disruption of the DEJ. Interestingly, despite the technological advantages, both HD-OCT and FD-OCT images showed lower prevalence of hyperkeratosis compared with TD-OCT. This finding may be because there were fewer studies that looked for the presence of hyperkeratosis compared with other features.

Studies investigating the morphological features of BCC seen on OCT imaging have shown similar levels of correlation with histopathological findings.^{8,34,35,37,38} Hussain *et al.*⁸ reviewed 17 papers on BCC features in OCT images and suggested that three could be used as diagnostic criteria: hyper-reflective border on the lateral portion of the tumour (noted in 53% of reviewed studies), hyporeflective nodules with peripheral rimming, and epidermal disarray (noted in all studies).

Another gauge of the diagnostic accuracy of OCT is its ability to delineate tumour margins. We analysed tumour depth data measured by OCT in comparison with the histopathological standard for 93 BCC tumours. Overall, we observed moderate correlation between OCT and histopathological depth. A possible contributor to the poorer depth characterization of OCT is the presence of inflammation in the tissue. Mogensen *et al.*³⁹ demonstrated that highly inflamed tissue may reduce image quality and render it more difficult to delineate the margins of the lesion for depth measurement. However, most of these cases occurred in the head and neck region, which is difficult to image accurately.³⁹

OCT machines have limited use at depths > 2 mm due to increased backscattering of light, making it difficult to obtain a clear image.⁵ This is evident in the results, which demonstrated reduced accuracy of OCT at lower depths, in terms of both concordance to depth category and percentage discrepancy from histopathological depth. It was also noted that deeper tumours tended to be underestimated, which is consistent with the depth limitations of OCT. Concordance and correlation tended to be higher at depths < 1.0 mm. However, percentage discrepancy was highest for tumours thinner than 0.5 mm in spite of a high concordance within this depth category. Likewise, the correlation coefficient at this depth category is unexpectedly low. These findings are likely due to the presence of three outliers that skewed the data. Another possible explanation is lack of adequate resolution of OCT technology to distinguish thin tumours directly below the surface of the skin, where significant artefacts from light scattering at the air-skin interface may occur.

Bland-Altman analysis demonstrated moderate agreement between measured (OCT) and true (histopathological) tumour depth. The deviations between these depth measurements tended to be smallest for thinner tumours and increased considerably for thicker tumours. There was also a slight trend towards underestimation of tumour depth by OCT for the thicker tumours. TD-OCT and FD-OCT exhibit similar levels of correlation between OCT and histopathological tumour depth despite the latter's technological advantages. Our dataset shows that TD-OCT tends to overestimate depth while FD-OCT generally underestimates it. Cheng and Guitera⁷ observed similar results in their review of seven studies, with correlations between OCT and histopathological depth ranging from 0.43 to 0.83. Additionally, more accurate depth measurements were found to be associated with thinner tumours.

When stratified based on anatomical site, the highest correlation between OCT and histopathological depth is for tumours on the extremities, with only 1% deviation from actual tumour depth. One explanation for these findings is that OCT imaging of the extremities is relatively simple in terms of manipulation of the probe on relatively flat surfaces. In contrast, the concave and convex contours of the head and neck hinder ideal probe placement, resulting in compromised images and poorer accuracy of depth prediction. This analysis is limited by the low number of tumours ($n = 24$) with available anatomical site data.

In summary, FD-OCT offers the highest diagnostic accuracy while HD-OCT provides the most effective visualization of BCC morphological features. TD-OCT tends to overestimate while FD-OCT underestimates tumour depth (Table S3; see Supporting Information).

One limitation of this review is the lack of control for interpreter skill level or mode of interpretation. A more experienced interpreter or one with more advanced training would presumably be better at detecting BCC features on OCT images. Given that OCT technology is relatively new and not

yet widely utilized, skill level among interpreters may vary greatly. This was demonstrated in a study³⁹ of the interpretation quality of 142 OCT images – skilled observers were able to diagnose BCC lesions with significantly higher sensitivity than untrained observers. With regards to mode of interpretation, no distinction was made between analysis using vertical cross-sectional images vs. horizontal cross-sectional images, the latter being offered only in FD-OCT and HD-OCT devices.

Another limitation is the broad categorization of OCT systems into TD-, HD- and FD-OCT. Some OCT machines contained modifications that enhanced their diagnostic accuracy, such as the use of speckle reduction, polarized light technology or dermoscopy in adjunct with OCT.^{14,41–43} These machines were analysed in aggregate with those that share the same baseline technology but lacked the above enhancements. Interpreter skill, modes of interpretation and OCT modifications are major factors contributing to a variation in the quality of data obtained from each study. Our study does not account for any clustering of tumour data that may have resulted from this.

In conclusion, based on primary tumour-level data from 31 studies encompassing 901 BCCs, our study demonstrated that OCT has high diagnostic accuracy for BCC. More advanced FD-OCT and HD-OCT systems, with improved resolution and depth penetration, outperformed TD-OCT in diagnostic accuracy and detection of BCC morphological features. Additional system enhancements are needed to improve the accuracy of tumour depth assessment.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Receiver operating characteristic curve describing the sensitivity against the specificity of optical coherence tomography for diagnosis of 477 basal cell carcinomas.

Table S1 Modified Newcastle–Ottawa Scale for noncomparative studies.

Table S2 Study characteristics.

Table S3 Summary of findings with respect to optical coherence tomography type.