Optical coherence tomography for the diagnosis of malignant skin tumors: a meta-analysis

Yi-Quan Xiong
Yun Mo
Yu-Qi Wen
Ming-Ji Cheng
Shu-Ting Huo
Xue-Jiao Chen
Qing Chen

Optical coherence tomography for the diagnosis of malignant skin tumors: a meta-analysis

Yi-Quan Xiong,† Yun Mo,† Yu-Qi Wen, Ming-Ji Cheng, Shu-Ting Huo, Xue-Jiao Chen, and Qing Chen*

Southern Medical University, School of Public Health, Guangdong Provincial Key Laboratory of Tropical Disease Research, Department of Epidemiology, Guangzhou, China

Abstract. Optical coherence tomography (OCT) is an emergent imaging tool used for noninvasive diagnosis of skin diseases. The present meta-analysis was carried out to assess the accuracy of OCT for the diagnosis of skin cancer. We conducted a systematic literature search through EMBASE, Medline, PubMed, the Cochrane Library, and Web of Science database for relevant articles published up to June 6, 2017. The quality of the included studies was assessed using the QUADAS-2 tool and the Oxford Levels of Evidence Scale. Statistical analyses were conducted using the software Meta-Disc version 1.4 and STATA version 12.0. A total of 14 studies involving more than 813 patients with a total of 1958 lesions were included in our analyses. The pooled sensitivity and specificity of OCT for skin cancer diagnoses were 91.8% and 86.7%, respectively. Subgroup analysis showed that the pooled sensitivities of OCT for detecting basal cell carcinoma (BCC), squamous cell carcinoma (SCC), actinic keratosis, and malignant melanoma were 92.4%, 92.3%, 73.8%, and 81.0%, respectively. The pooled specificities were 86.9%, 99.5%, 91.5%, and 93.8%, respectively. OCT appears to be useful for the detection of BCC and SCC. It is a valuable diagnostic method when screening for early skin cancers. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE)

Keywords: optical coherence tomography; skin cancer; basal cell carcinoma; squamous cell carcinoma; actinic keratosis; malignant melanoma.

1 Introduction

Alarming increases in the incidence and prevalence of malignant skin tumors have occurred in recent decades, especially for malignant melanoma (MM), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC).1–4 Nonmelanoma skin cancers (NMSC), including Bowen’s disease, actinic keratosis (AK), BCC, and SCC, are the most prevalent malignancies affecting light-skinned individuals worldwide and represent almost 95% of all cutaneous cancer diagnoses.5–8 The World Health Organization reported an increase of more than 2 to 3 million new cases of NMSC per year, of which about 80% are BCCs.9–11 Meanwhile, MM is also increasing in frequency both in the UK and Europe.12 MM accounts for 2% of skin cancers and is responsible for nearly 1% of deaths caused by oncological etiologies.13 Both NMSC and MM have excellent prognosis when they are diagnosed and treated early.14 If melanoma is treated while in situ or stage 1, the overall 5-year survival rate is over 90%, but for metastatic disease at stage 4, the rate drops rapidly to 10% to 15%.11 Thus, diagnosis at an early stage is crucial for improving survival rates and overall prognosis,12–14 and it is important that dermatologists not only provide preventative counseling but also be astute in the early diagnosis and treatment of any suspected malignancies.15

Several new methods offer improved diagnoses of skin lesions.16 In particular, the development of optospectral technologies for imaging of living tissues is reshaping the dermatological practice. This technique offers in vivo/ex vivo, noninvasive, painless, real-time visualization of skin structures and physiological parameters, at high resolution and without interfering with the morphology and the functions of the examined integument.17–19

Optical coherence tomography (OCT) was first used medically in 1988 in ophthalmology by Fercher et al.20 This method is based on the physical principle of low-coherence interferometry and uses infrared light21 to measure the scattering properties of tissues (echo time delay and the intensity of backscattered or back-reflected light).22–24 It provides a real-time, cross-sectional as well as en-face sectional images of the subsurface microstructure of tissues with micrometer resolution, enabling visualization of skin morphology (epidermis, dermis, dermoeidermal junction, nodular and fibrous structures, cellular elements, hair follicle units, blood vessels, and sweat glands) and investigation of the altered skin architecture present in superficial skin lesions.13,19,25,26 High-definition OCT (HD-OCT) is a technique based on the principal of conventional OCT using a combination of parallel time-domain interferometry and adaptive optics.27 Conventional OCT techniques, such as VivoSight OCT, polarized sensitivity OCT (PS-OCT), Skintell HD-OCT, or full-field OCT (FF-OCT), offer two-dimensional (brightness-scan mode) and three-dimensional (3-D) (c-scan mode) reconstruction of the images with acquisition speeds reported to be up to several volumes per second, as well as noise removal.28

In recent years, it has been demonstrated that melanocytic lesions such as AK, SCC, and BCC have distinctive features revealed using OCT that can differentiate them from noncancerous skin lesions.29–32 However, the reported diagnostic accuracy of OCT is inconsistent. To formulate a comprehensive basis for use of OCT, we performed a meta-analysis of the literature to assess OCT for differentiating skin tumors from normal skin.

2 Methods

This meta-analysis was conducted according to the published standards for reviews of diagnostic accuracy and performed...
in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.33

2.1 Literature Search

Electronic searches were conducted of EMBASE, Medline, PubMed, the Cochrane Library, and the Web of Science databases from the earliest date available until June 6, 2017. We used the following key words, separately and in combination: “skin,” “tumor,” “cancer,” “neoplasm,” “carcinoma,” “melanoma,” “basal cell carcinoma,” “BCC,” “squamous cell carcinoma,” “SCC,” “optical coherence tomography,” and “OCT.” No language restriction was applied to the searches, but the search was restricted to studies on humans. Forward citation searching of the reference lists of the original studies and review articles was also conducted.

2.2 Eligibility Criteria

Studies were screened for eligibility using the following criteria: (i) evaluation by diagnostic clinical trials of the accuracy of OCT for the diagnosis of skin cancer in patients, (ii) retrospective or prospective study design, (iii) results reported with sufficient data to construct a diagnostic $2 \times 2$ contingency table, including true-positive, false-positive, true-negative, and false-negative data, and (iv) all diagnoses were confirmed by the histology seen in a biopsy sample. Comment papers, small case series, case reports, reviews, or guideline articles were excluded. When more than one article reported the same study, the publication with more information was selected.

2.3 Data Selection and Extraction

Citations were merged in EndNote (version X7) to facilitate management. Two authors independently evaluated all retrieved articles by title and abstract according to the previous inclusion criteria in a nonblinded, standardized manner. After full-text screening, articles that fulfilled the inclusion criteria were selected for the final analysis. Data were extracted from each eligible study by two authors independently and a consensus was reached on all items. Relevant data included: (i) first author, year of publication, country of origin, study design (prospective or retrospective), number of centers; (ii) type of OCT system, (iii) in vivo or ex vivo examination; (iv) type of skin cancer; (v) number of investigators and their experience, OCT analysis (blinded or others); (vi) number of enrolled patients and specimens, baseline patient characteristics (age distribution and sex ratio); and (vii) accuracy of OCT (sensitivity and specificity) with reference to histopathology.

2.4 Quality Assessment

The quality of the included studies and the risk of bias were assessed according to the Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009)34 and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)35 tools by two authors independently. QUADAS-2 consists of four key domains regarding patient selection, index test, reference standard, and flow of patients (through the study and timing of the index tests). Risk of bias was judged as “low,” “high,” and “unclear.”
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Center (n)</th>
<th>Type of OCT</th>
<th>Type of cancer</th>
<th>Investigators</th>
<th>Experienced</th>
<th>Patients (n)</th>
<th>Age (mean or median)</th>
<th>Male (%)</th>
<th>Lesions</th>
<th>Levels of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gambichler et al.</td>
<td>2015</td>
<td>Germany</td>
<td>Pro</td>
<td>Three</td>
<td>Skintell HD-OCT</td>
<td>MM</td>
<td>One</td>
<td>Exp</td>
<td>64</td>
<td>NA NA</td>
<td>93</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Hussain et al.</td>
<td>2016</td>
<td>Denmark</td>
<td>Pro</td>
<td>One</td>
<td>VivoSight OCT</td>
<td>BCC</td>
<td>NA</td>
<td>NA</td>
<td>58</td>
<td>65.9 (41 to 88)</td>
<td>37.5</td>
<td>58</td>
<td>1b</td>
</tr>
<tr>
<td>Mogensen et al.</td>
<td>2009</td>
<td>Denmark</td>
<td>Retro</td>
<td>One</td>
<td>OCT and PS-OCT</td>
<td>NMSC</td>
<td>Two</td>
<td>Exp</td>
<td>104</td>
<td>69.3 (37 to 90)</td>
<td>43.0</td>
<td>220</td>
<td>1b</td>
</tr>
<tr>
<td>Markowitz et al.</td>
<td>2015</td>
<td>USA</td>
<td>Pro</td>
<td>Three</td>
<td>VivoSight OCT</td>
<td>BCC</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>115</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Maier et al.</td>
<td>2014</td>
<td>Germany</td>
<td>Pro</td>
<td>One</td>
<td>Skintell HD-OCT</td>
<td>BCC</td>
<td>One</td>
<td>Exp</td>
<td>20</td>
<td>NA (53 to 90)</td>
<td>55.0</td>
<td>80</td>
<td>1b</td>
</tr>
<tr>
<td>Durkin et al.</td>
<td>2014</td>
<td>USA</td>
<td>Retro</td>
<td>One</td>
<td>FF-OCT</td>
<td>SCC, BCC</td>
<td>One</td>
<td>NA</td>
<td>11</td>
<td>70 (33 to 90)</td>
<td>64.2</td>
<td>18</td>
<td>1b</td>
</tr>
<tr>
<td>Ulrich et al.</td>
<td>2015</td>
<td>Germany</td>
<td>Pro</td>
<td>Six</td>
<td>VivoSight OCT</td>
<td>BCC</td>
<td>NA</td>
<td>Exp</td>
<td>155</td>
<td>NA</td>
<td>235</td>
<td>1a</td>
<td></td>
</tr>
<tr>
<td>Wahrlich et al.</td>
<td>2015</td>
<td>Germany</td>
<td>Pro</td>
<td>One</td>
<td>VivoSight OCT</td>
<td>BCC</td>
<td>One</td>
<td>Exp</td>
<td>50</td>
<td>62.8</td>
<td>46.0</td>
<td>50</td>
<td>1b</td>
</tr>
<tr>
<td>Boone et al.</td>
<td>2016</td>
<td>Denmark</td>
<td>Pro</td>
<td>One</td>
<td>Skintell HD-OCT</td>
<td>AK, SCC</td>
<td>NA</td>
<td>NA</td>
<td>108</td>
<td>66.3 (39 to 92)</td>
<td>47.8</td>
<td>108</td>
<td>1b</td>
</tr>
<tr>
<td>Marvdashti et al.</td>
<td>2016</td>
<td>USA</td>
<td>Retro</td>
<td>One</td>
<td>PS-OCT</td>
<td>BCC</td>
<td>One</td>
<td>Exp</td>
<td>42</td>
<td>NA NA</td>
<td>520</td>
<td>1b</td>
<td></td>
</tr>
<tr>
<td>Olsen et al.</td>
<td>2016</td>
<td>Denmark</td>
<td>Pro</td>
<td>One</td>
<td>VivoSight OCT</td>
<td>AK, BCC</td>
<td>Five</td>
<td>Exp</td>
<td>NA</td>
<td>69.4</td>
<td>54.9</td>
<td>142</td>
<td>1b</td>
</tr>
<tr>
<td>Boone et al.</td>
<td>2016</td>
<td>Denmark</td>
<td>Retro</td>
<td>One</td>
<td>Skintell HD-OCT</td>
<td>MM</td>
<td>NA</td>
<td>NA</td>
<td>45</td>
<td>51 (20 to 70)</td>
<td>44.4</td>
<td>45</td>
<td>1b</td>
</tr>
<tr>
<td>Maneffe et al.</td>
<td>2016</td>
<td>Belgium</td>
<td>Retro</td>
<td>One</td>
<td>Skintell HD-OCT</td>
<td>AK, SCC</td>
<td>Three</td>
<td>Exp</td>
<td>71</td>
<td>66.9 (35 to 91)</td>
<td>50.7</td>
<td>106</td>
<td>1b</td>
</tr>
<tr>
<td>Cheng et al.</td>
<td>2016</td>
<td>Australia</td>
<td>Pro</td>
<td>One</td>
<td>OCT</td>
<td>BCC</td>
<td>Three</td>
<td>Exp</td>
<td>103</td>
<td>66 (31 to 88)</td>
<td>61.2</td>
<td>168</td>
<td>1b</td>
</tr>
</tbody>
</table>

Note: OCT, optical coherence tomography; HD-OCT, high-definition OCT; PS-OCT, polarized sensitivity OCT; MM, malignant melanoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; AK, actinic keratosis; NMSC, nonmelanoma skin cancer; AHM, amelanotic/hypomelanotic melanoma; NA, no data available; Pro, prospective; Retro, retrospective; and Exp, experienced.
2.5 Statistical Analysis

Sensitivity, specificity, positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were meta-analyzed. Between-study heterogeneity was estimated by $I^2$ statistics; significant heterogeneity was defined as $I^2 > 50\%$. Pooled results and their corresponding 95% confidence intervals (CIs) were calculated with a fixed-effects model (Mantel and Haenszel method) when heterogeneity was not significant ($I^2 < 50\%$); otherwise, a random-effects model (DerSimonian and Laird method) was applied. Forest plots were constructed for visual display of pooled results if necessary. A weighted symmetric summary receiver operating characteristic (sROC) curve was drawn, and the area under the curve (AUC) was calculated. Threshold analysis was performed using the Spearman’s coefficient ($>0.5$ with $p < 0.05$). Meta-regression was also performed to explore the potential heterogeneity among studies. Statistical analyses were conducted using Meta-Disc software (version 1.4; Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain). Publication bias was assessed using STATA (version 12.0; Stata Corp; College Station, Texas), and the Midas command was used for all statistical analyses.

3 Results

3.1 Description of the Included Studies

The initial search yielded 2773 references, of which 1621 potentially relevant studies were unique. Fourteen studies\(^{1,12,13,39-49}\) including eight prospective and six retrospective studies, that involved more than 813 patients and 1958 lesions were included in the final analysis. The selection process for the studies is shown in Fig. 1. The main characteristics of the 14 studies\(^{1,12,13,39-49}\) are summarized in Table 1. All of the studies were conducted in the USA, Germany, Belgium, Australia, and Denmark, and three were multicenter studies.\(^{12,39,42}\) Five studies used VivoSight OCT,\(^{1,39,42,43,46}\) five used Skintell HD-OCT,\(^{1,2,40,44,45,50}\) two used PS-OCT,\(^{13,47}\) and the remaining one used FF-OCT.\(^{51}\) All included studies covered most types of skin cancer, including MM, AK, BCC, and SCC. Twelve studies\(^{1,12,13,39-42,44-48}\) reported the diagnostic performance of OCT in differentiating cancerous from noncancerous skin, and some studies validated the distinction of BCC,\(^{1,39,43,46,47,49,50}\) SCC,\(^{41,44,46,48}\) AK,\(^{44,46,48}\) or MM\(^{12,45}\) from other cancerous or noncancerous lesions, respectively. Three studies\(^{43,47,48}\) used a newly developed scoring systems [the “Berlin score” (BS)] or algorithms as assisting tools in detection. Nine studies\(^{12,13,40,42,44,46,47,49}\) noted the experience of the observers who examined the outcomes of OCT images.

3.2 Quality Assessment

Two scales were used for assessing the study quality. The results assessed using the Oxford Levels of Evidence Scale are shown in Table 1, and the results assessed using QUADAS-2 are shown in Table 2. Most of the studies included in our analysis were of high quality. One study\(^{13}\) had a high risk of bias in patient selection because normal adjacent skin areas were selected to use as the control sites. Four studies, in which some patients were excluded from the final analysis because of lack of information\(^ {1,42}\) or absence of optimal quality OCT images,\(^{13,47}\) were classified as having a high risk of bias in flow and timing. And in one

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias</th>
<th>Applicability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>Index test</td>
<td>Reference standard</td>
</tr>
<tr>
<td>Flow and timing</td>
<td>Patient selection</td>
<td>Index test</td>
</tr>
<tr>
<td>Gambichler et al.(^{12})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hussain et al.(^{1})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Mogensen et al.(^{13})</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Markowitz et al.(^{39})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Maier et al.(^{40})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Durkin et al.(^{41})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ulrich et al.(^{42})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Wahrlich et al.(^{43})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Boone et al.(^{44})</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Marvdashti et al.(^{47})</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Olsen et al.(^{46})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Boone et al.(^{48})</td>
<td>Low</td>
<td>Unclear</td>
</tr>
<tr>
<td>Marneffe et al.(^{44})</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Cheng et al.(^{49})</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Note: Low, low risk; High, high risk; and Unclear, unclear risk.
study, 44 the control patients did not have the same reference standards as the cases, suggesting a high risk of selection bias.

### 3.3 Diagnostic Accuracy of OCT for Skin Cancer

Twelve studies, 1,12,13,39–42,44–48 including a total of 1740 lesions, reported the diagnostic accuracy of OCT for distinguishing cancerous from noncancerous features at the per-lesion level. The sensitivity ranged from 66.7% to 100.0% and specificity ranged from 64.4% to 100.0%. The corresponding pooled sensitivity and specificity were 91.8% (95% CI: 0.90 to 0.94, \( I^2 = 72.9\% \)) and 86.7% (95% CI: 0.84 to 0.89 \( I^2 = 85.5\% \)), respectively (Fig. 2). The pooled PLR and NLR were 6.94 (95% CI: 4.21 to 11.47, \( I^2 = 86.3\% \)) and 0.12 (95% CI: 0.07 to 0.20, \( I^2 = 79.1\% \)), respectively. The AUC for sROC was 0.95 (Fig. 3).

The distribution of scatter points in the sROC was not in a shoulder-like form and the Spearman’s coefficient was 0.14 (\( p = 0.67 \)), suggesting that there was no threshold effect.

### 3.4 Diagnostic Accuracy of OCT for BCC

Nine studies, 1,39–43,46,47,49 covering a total of 1386 lesions, reported the diagnoses of BCC by OCT. The pooled sensitivity was 92.4% (95% CI: 0.90 to 0.94, \( I^2 = 71.7\% \)) and specificity was 86.9% (95% CI: 0.84 to 0.89, \( I^2 = 89.4\% \)); whereas the pooled PLR and NLR were 6.07 (95% CI: 4.21 to 11.47, \( I^2 = 88.9\% \)) and 0.12 (95% CI: 0.07 to 0.20, \( I^2 = 80.3\% \)), respectively. The AUC for sROC was 0.95 (Table 3).

### 3.5 Diagnostic Accuracy of OCT for SCC

Three studies, 41,44,48 including the diagnoses of SCC, achieved a pooled sensitivity of 92.3% (95% CI: 0.79 to 0.98, \( I^2 = 71.2\% \)) and a high specificity of 99.5% (95% CI: 0.97 to 1.00, \( I^2 = 0.0\% \)); then the pooled PLR and NLR were...
Table 3  Subgroup analysis of some important indices (with 95% CIs).

<table>
<thead>
<tr>
<th>Kind of cancer</th>
<th>Number of studies (lesions)</th>
<th>Sensitivity (95% CI, %)</th>
<th>Heterogeneity ($I^2$) (%)</th>
<th>Specificity (95% CI, %)</th>
<th>Heterogeneity ($I^2$) (%)</th>
<th>Positive LR (95% CI)</th>
<th>Heterogeneity ($I^2$) (%)</th>
<th>Negative LR (95% CI)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC</td>
<td>9 (1386)</td>
<td>92.4% (90.3 to 94.3)</td>
<td>71.7</td>
<td>86.9% (84.1 to 89.4)</td>
<td>89.4</td>
<td>6.07 (3.27 to 11.3)</td>
<td>88.9</td>
<td>0.12 (0.07 to 0.23)</td>
<td>80.3 0.95</td>
</tr>
<tr>
<td>SCC</td>
<td>3 (232)</td>
<td>92.3% (79.1 to 98.4)</td>
<td>71.2</td>
<td>99.5% (97.1 to 100.0)</td>
<td>0.0</td>
<td>68.01 (17.0 to 272)</td>
<td>0.0</td>
<td>0.11 (0.01 to 1.20)</td>
<td>82.0 1.00</td>
</tr>
<tr>
<td>AK</td>
<td>3 (356)</td>
<td>73.8% (66.5 to 80.3)</td>
<td>96.7</td>
<td>91.5% (86.5 to 95.1)</td>
<td>0.0</td>
<td>7.67 (3.94 to 14.9)</td>
<td>40.4</td>
<td>0.17 (0.02 to 1.34)</td>
<td>96.4 0.97</td>
</tr>
<tr>
<td>MM</td>
<td>2 (138)</td>
<td>81.0% (65.9 to 91.4)</td>
<td>62.3</td>
<td>93.8% (86.9 to 97.7)</td>
<td>0.0</td>
<td>11.82 (5.16 to 27.0)</td>
<td>3.4</td>
<td>0.18 (0.05 to 0.71)</td>
<td>54.0 0.5</td>
</tr>
<tr>
<td>In/ex vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vivo</td>
<td>9 (1122)</td>
<td>91.6% (89.0 to 93.8)</td>
<td>61.7</td>
<td>84.1% (80.8 to 87.1)</td>
<td>76.4</td>
<td>6.35 (4.30 to 9.39)</td>
<td>68.6</td>
<td>0.11 (0.07 to 0.17)</td>
<td>51.4 0.95</td>
</tr>
<tr>
<td>Ex vivo</td>
<td>3 (618)</td>
<td>92.1% (88.5 to 94.9)</td>
<td>89.6</td>
<td>91.1% (87.4 to 94.0)</td>
<td>93.9</td>
<td>7.75 (0.80 to 75.2)</td>
<td>99.6</td>
<td>0.19 (0.04 to 1.00)</td>
<td>94.8 0.93</td>
</tr>
<tr>
<td>Type of OCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conventional OCT</td>
<td>6 (1290)</td>
<td>93.4% (91.2 to 95.2)</td>
<td>59.0</td>
<td>86.7% (83.9 to 89.2)</td>
<td>90.5</td>
<td>6.93 (3.59 to 13.4)</td>
<td>90.6</td>
<td>0.08 (0.05 to 0.14)</td>
<td>58.5 0.97</td>
</tr>
<tr>
<td>HD-OCT</td>
<td>6 (450)</td>
<td>87.9% (82.9 to 91.9)</td>
<td>73.8</td>
<td>86.8% (81.7 to 90.9)</td>
<td>79.6</td>
<td>7.65 (2.98 to 19.6)</td>
<td>80.8</td>
<td>0.18 (0.09 to 0.36)</td>
<td>72.7 0.94</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospectively</td>
<td>6 (723)</td>
<td>90.6% (86.9 to 93.5)</td>
<td>77.4%</td>
<td>78.4% (74.0 to 82.4)</td>
<td>80.5</td>
<td>4.25 (2.85 to 6.33)</td>
<td>72.9</td>
<td>0.13 (0.06 to 0.30)</td>
<td>78.6 0.91</td>
</tr>
<tr>
<td>Retrospectively</td>
<td>6 (999)</td>
<td>92.5% (90.0 to 94.6)</td>
<td>71.3%</td>
<td>93.5% (90.9 to 95.5)</td>
<td>29.5</td>
<td>12.08 (7.77 to 18.8)</td>
<td>27.8</td>
<td>0.10 (0.05 to 0.21)</td>
<td>78.9 0.97</td>
</tr>
<tr>
<td>Experienced/NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experienced</td>
<td>7 (1396)</td>
<td>91.2% (88.8 to 93.2)</td>
<td>79.8</td>
<td>86.0% (83.3 to 88.5)</td>
<td>90.8</td>
<td>6.09 (3.18 to 11.6)</td>
<td>91.9</td>
<td>0.13 (0.07 to 0.25)</td>
<td>84.8 0.94</td>
</tr>
<tr>
<td>NA</td>
<td>5 (344)</td>
<td>93.9% (89.6 to 96.8)</td>
<td>56.6</td>
<td>89.8% (83.7 to 94.2)</td>
<td>53.4</td>
<td>8.18 (4.38 to 15.3)</td>
<td>27.8</td>
<td>0.09 (0.03 to 0.26)</td>
<td>69.5 0.97</td>
</tr>
</tbody>
</table>

Note: AUC, area under the curve; CI, confidence interval; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; AK, actinic keratosis; MM, malignant melanoma; OCT, optical coherence tomography; HD-OCT, high-definition OCT; and NA, no data available.
68.01 (95% CI: 17.01 to 272.4, \( I^2 = 0.0\% \)) and 0.11 (95% CI: 0.01 to 1.20, \( I^2 = 82.0\% \)), respectively. The AUC for sROC was 1.00 (Table 3).

### 3.6 Diagnostic Accuracy of OCT for AK

Three studies\(^{44,46,48}\) addressed the diagnosis of AK with pooled sensitivity and specificity of 73.8% (95% CI: 0.67 to 0.91, \( I^2 = 96.7\% \)) and 91.5% (95% CI: 0.87 to 0.95, \( I^2 = 0.0\% \)), respectively. The pooled PLR and NLR were 7.67 (95% CI: 3.94 to 14.94, \( I^2 = 40.4\% \)) and 0.17 (95% CI: 0.02 to 1.34, \( I^2 = 96.4\% \)), respectively. The AUC for sROC was 0.97 (Table 3).

### 3.7 Diagnostic Accuracy of OCT for MM

Only two publications\(^{12,25}\) reported diagnoses of MM and achieved 81.0% (95% CI: 0.66 to 0.91, \( I^2 = 62.3\% \)), 93.8% (95% CI: 0.87 to 0.98, \( I^2 = 0.0\% \)), 11.82 (95% CI: 5.16 to 27.09, \( I^2 = 3.4\% \)), and 0.18 (95% CI: 0.05 to 0.71, \( I^2 = 54.0\% \)) for the pooled sensitivity, specificity, PLR, and NLR, respectively (Table 3).

### 3.8 Heterogeneity Analysis

Between-study heterogeneity of the 12 studies that reported diagnostic accuracy of OCT for skin cancers was explored using subgroup analyses classified by types of OCT (HD-OCT or conventional OCT), study design (prospective versus retrospective), and diagnosis mode (in vivo versus ex vivo).

Six studies used HD-OCT, such as Skintell HD-OCT\(^{12,40,44,45,48}\) and FF-OCT\(^{41}\), the other six studies used conventional OCT, including VivoSight OCT\(^{1,39,42,46}\) and PS-OCT\(^{13,47}\). The pooled sensitivity of HD-OCT was 87.9% (95% CI: 0.83 to 0.92, \( I^2 = 73.8\% \)), which was slightly lower than that of conventional OCT at 93.4% (95% CI: 0.92 to 0.95, \( I^2 = 59.0\% \)). However, the pooled specificity of HD-OCT was similar to that of conventional OCT (86.8% (95% CI: 0.82 to 0.91, \( I^2 = 79.6\% \)) versus 86.7% (95% CI: 0.84 to 0.89, \( I^2 = 90.5\% \)) (Table 3).

Moreover, the pooled sensitivity of nine studies with in vivo data\(^{12,13,39,42,44,46,48}\) and three with ex vivo data\(^{46,41,47}\) imaging was 91.6% (95% CI: 0.89 to 0.94, \( I^2 = 62.3\% \)) and 92.1% (95% CI: 0.89 to 0.95, \( I^2 = 89.6\% \)); their pooled specificity was 84.1% (95% CI: 0.81 to 0.87, \( I^2 = 76.4\% \)) and 91.1% (95% CI: 0.87 to 0.94, \( I^2 = 93.9\% \)), respectively (Table 3).

We also conducted a meta-regression to explore potential heterogeneity. In the meta-regression, we included six variables: (i) diagnosis mode (in vivo versus ex vivo), (ii) number of lesions (≥50 versus <50), (iii) study center (single versus multiple), (iv) type of cancer, (v) observer’s experience (experienced versus nonexperienced), and (vi) type of OCT (HD-OCT versus conventional OCT). The meta-regression analysis failed to reveal any factor that contributed to the heterogeneity.

### 3.9 Publication Bias

The funnel plots for publication bias were symmetrical, and Deek’s test indicated no statistically significant publication bias (\( p = 0.19 \)).

### 4 Discussion

Dermoscopy is a widely used method for the clinical diagnosis of skin diseases.\(^{12}\) A meta-analysis reported the diagnostic accuracy of dermoscopy has a sensitivity of 83.2% and specificity of 85.8%,\(^{51}\) which were both superior to the diagnostic accuracy achieved with the unaided eye. Among high-resolution optical imaging technologies, reflectance confocal microscopy (RCM) is reported to be one of the best techniques for noninvasive diagnosis.\(^{12}\) Previous reports have demonstrated that RCM has a sensitivity of 94% and specificity of 83% for skin cancer diagnoses.\(^{12,52}\) However, as one of the most time-consuming and costly diagnostic methods, RCM can be difficult to apply in daily practice.\(^{12,52}\) OCT is an alternative method with the advantage of avoiding pre- and posttreatment biopsies. Moreover, functional quantitative information can be extracted (that is, flow information, layer thickness, and attenuation coefficient of the OCT signal).\(^{53,54}\) To the best of our knowledge, this is the first meta-analysis on the accuracy of OCT technique in diagnosing skin tumors. We assessed the accuracy of OCT in detecting dermatologic lesions as reported in 14 studies involving more than 813 patients and 1958 lesions. Our results indicate that OCT can accurately differentiate cancers from noncancerous lesions with a pooled sensitivity of 91.8% (95% CI: 0.90 to 0.94) and specificity of 86.7% (95% CI: 0.84 to 0.89), values that are higher than those of dermoscopy,\(^{51}\) and approximately equal to those of RCM.\(^{12,52}\)

BCC is one of the most common skin cancers, with a prevalence exceeding all other skin cancers combined. Most clinical studies of OCT are focused on diagnostic accuracy for BCC, and they report a sensitivity of 79% to 94% and specificity of 85% to 96%.\(^{15}\) From our analysis, the pooled sensitivity and specificity of OCT for BCC were 92.4% (95% CI: 0.90 to 0.94) and 86.9% (95% CI: 0.87 to 0.89), respectively. Additionally, we assessed the diagnostic accuracy of OCT for SCC, AK, and MM, with a pooled sensitivity of 92.3% (95% CI: 0.79 to 0.99), 73.8% (95% CI: 0.67 to 0.80), and 81.0% (95% CI: 0.66 to 0.92), respectively. Similarly, the specificities for the diagnoses were 99.5% (95% CI: 0.97 to 1.00) for SCC, 91.5% (95% CI: 0.87 to 0.96) for AK, and 93.8% (95% CI: 0.87 to 0.98) for MM.

Several studies reported that the main limitation of OCT for diagnosing BCC is an inability to identify its subtypes.\(^{13,16}\) This may suggest that the diagnostic features of BCC are too subtle to recognize in the OCT images.\(^{56}\) Cheng et al.\(^{56}\) reported that the sensitivity and specificity of OCT for superficial BCC were 87.0% and 80.0%, respectively, which indicated that the improvements of the OCT technique now allow detailed imaging of structures within the uppermost layers of the skin, and have made it possible to identify the morphology of the different subtypes of BCC in the clinic.\(^{55,56}\) Newer studies are focusing on determining diagnostic accuracy based on scoring systems\(^{43}\) or algorithms\(^{45,46}\) as adjunctive tools in the clinical setting. Wahrlich et al.\(^{41}\) validated diagnostic BCC using OCT with a newly developed scoring system (BS). Their study found that application of the OCT by students revealed a sensitivity and specificity of 92.8% and 24.1%, respectively. However, the sensitivity and specificity amounted to 96.6% and 75.2% when the OCT used by dermatological specialists and experts, showing that experience markedly increased the sensitivity and specificity of the diagnosis of BCC.

The thickness of BCC is an important prognostic factor. A study of 127 BCC patients treated with imiquimod showed a recurrence rate of 58% in lesion thickness >0.40 mm, whereas
there was no recurrence in lesion thickness ≤0.4 mm (mean fol-
low-up period 34 months). However, it is difficult to accurately
determine the thickness of BCC tumors using clinical examina-
tion alone. OCT provides a useful tool for depth measurement of
BCC thickness, particularly for thin tumors <0.4 mm. Cheng
et al. reported that there was excellent correlation between
OCT and biopsy for tumor depth among ≤0.4 mm (Pearson’s
 correlation r = 0.86, p < 0.001), but the correlation was becom-
ing smaller with increase of the depth of thickness. Therefore,
the use of OCT can guide an appropriate treatment for BCC
based on tumor thickness.

The conventional OCT system has a penetration depth of up
to 2 mm, with an optical lateral resolution of at least 7.5 μm and
axial resolution of at least 5 μm. The HD-OCT devices pos-
sess a scan area of 1.8 × 0.5 mm and a penetration depth of 450
to 750 μm in optimal conditions. Although HD-OCT has a
lower penetration depth than conventional OCT, it provides
imaging with a higher lateral and axial resolution of about 3 μm,
making it possible to visualize specific 3-D image details in
either mode (i.e., en-face visualization in slice mode and vice
versa) with real-time scanning. Nonetheless, it seems that the
diagnostic limitations of HD-OCT are such that it cannot
reliably rule out melanoma based on a morphology
analysis. Our subgroup analysis found that HD-OCT has a
sensitivity of 87.9%, which was lower than that of conventional
OCT (93.4%), whereas the specificity of HD-OCT was similar to
conventional OCT (86.8 versus 86.7%).

There is a limited penetration depth for in vivo examination
(<1 mm), which does not allow a complete evaluation of the
tumor depth, whereas in ex vivo imaging, the scanning process is
not limited to a certain depth. In a recent study, OCT was
applied ex vivo in the detection of BCC on frozen sections pre-
pared for Mohs micrographic surgery and resulted in a low
specificity (56%) and low sensitivity (19%). This result
derived mainly from the reduced contrast in OCT images that
have previously been noted in ex vivo samples and possibly
as a result of increased optical scatter in nonperfused tissue.
Our study shows that the sensitivity of ex vivo and in vivo detec-
tion was 92.1% and 91.6%, and the specificity was 91.1% and
84.1%, respectively. The field of ex vivo imaging is rapidly
evolving, and perhaps the next generation of devices will cap-
ture sufficient nuclear detail.

Use of noninvasive techniques for determining the depth of
BCC thickness would obviate the need for invasive tissue
biopsy. Cheng et al. reported that there was a potential 76%
reduction of biopsy with a 5% error rate using OCT. Ulrich
et al. found that the diagnostic accuracy of BCC increased from
65.8% (clinical) to 76.2% (clinical + dermoscopy) to 87.4% (clinical + dermoscopy + OCT). Markowitz et al. also
found that the overall diagnostic accuracy was 57% with
clinical examination alone; however, the rate rose to 70% with
dermoscopy and 88% with OCT, and the results showed
that more than 1 in 3 patients would avoid diagnostic biopsy
in combination of these three methods by the improved
specificity.

As previous studies have reported, OCT has several primary
benefits for clinical practice. First, OCT can increase the diag-
noses of cancerous lesions and reduce the incidence of false-
negative examinations. Second, by identifying lesions earlier,
treatment measures can be initiated in a timely manner, with
improved clinical and cosmetic outcomes and reduced
morbidity. Third, OCT could provide information on
tumor margins and depth, so that surgical interventions can be
planned better. Fourth, OCT may complement other im-
aging methods, such as RCM or dermoscopy. Fifth, OCT could
monitor the progress of noninvasive treatment. Sixth, OCT
could reduce biopsy. OCT with sophisticated lasers has not
yet achieved cellular resolution images, although its imaging
characteristics indicate that this should be possible. In one study
to assess OCT imaging in the diagnosis of NMSC, 59% of the
lesions were discarded, mainly as a result of artifacts caused by
too little gel, hyperkeratosis, motion, and mismatch of the probe
and skin. These findings suggest that refining OCT diagnostic
criteria and improving image quality and resolution can
increase diagnostic accuracy.

We reported results of diagnostic accuracy of OCT for skin
tumors in the meta-analysis, including the limitations and poten-
tial biases. The sources of bias include variation in (i) study
design, (ii) inclusion and exclusion criteria, (iii) type of OCT
device, and (iv) the clinical experience of the observer. One
study met our inclusion criteria but was excluded because the
images obtained in more than half of the cases were inade-
quate. The aforementioned contribute to heterogeneity.
Although we used a random-effects model, between-study
variation was taken into account, and there was still some
influence on the results. In addition, not all the studies were of
high quality, which might lead to some bias in the final statistical
results.

5 Conclusions
OCT appears to have significant potential for improving diag-
nosis of BCC and SCC, and for monitoring and therapy of skin
cancers. Combinations of OCT with other imaging techniques,
such as RCM, refining the OCT morphological diagnostic
criteria, as well as improving image quality and resolution of OCT
images could improve our capability to easily and accurately
diagnose many skin cancers.

Disclosures
No conflicts of interest, financial or otherwise, are declared by
the authors.

Compliance with Ethical Standards
This article does not contain any studies with human participants
performed by any of the authors.

References
1. A. A. Hussain et al., “Adjunct use of optical coherence tomography
increases the detection of recurrent basal cell carcinoma over clinical
dermoscopic examination alone,” Photodiagn. Photodyn. Ther. 14,
2. F. Birch-Johansen et al., “Trends in the incidence of nonmelanoma skin
cancer in Denmark 1978–2007: rapid incidence increase among young
4. M. Trakatelli et al., “Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective
6. C. A. Banzhaf et al., “Optical coherence tomography imaging of non-
melanoma skin cancer undergoing imiquimod therapy,” Skin Res.


Yi-Quan Xiong is a doctoral candidate at the Southern Medical University, who majored in clinical epidemiology and evidence-based medicine. He has published several system reviews focusing on the application of optical imaging technology in tumor diagnosis.

Biographies for the other authors are not available.