Diagnostic accuracy of optical coherence tomography in bladder cancer patients: A systematic review and meta-analysis

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Received June 24, 2017; Accepted September 28, 2017

DOI: 10.3892/mco.2018.1566

Abstract. A meta-analysis was performed to evaluate the accuracy of optical coherence tomography (OCT) for diagnostic accuracy studies in bladder cancer patients. English language studies reporting the diagnostic accuracy of OCT for bladder cancer were retrieved from the PubMed, EMBASE and Cochrane Library databases in December 2014. Histopathology was a reference standard. Sensitivities, specificities, positive likelihood ratios and negative likelihood ratios were calculated, and summary receiver operating characteristic curves were drawn to determine the diagnostic accuracy of OCT. Finally, 9 eligible studies (468 patients) were included in our meta-analysis. The pooled sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of OCT were 0.96 [95% confidence interval (CI): 0.94-0.98], 0.82 (95% CI: 0.80-0.85), 6.83 (95% CI: 3.24-14.1) and 0.05 (95% CI: 0.02-0.16), respectively. The summary diagnostic odds ratio was 138.88 (95% CI: 29.63-650.89) and the overall area under the curve was 0.9735. These results suggest that OCT has excellent diagnostic performance in patients with bladder cancer and recurrent lesions.

Introduction

Bladder cancer is the most common urothelial carcinoma, with its incidence being fourth in men and tenth in women among all cancers. Despite recent advances in this field, the death rate remains relatively high. Even 70% of superficial bladder tumors have a propensity for recurrence or progression within 5 years (1,2). However, patients with bladder cancer are curable if diagnosed and treated early. Thus, a major concern for patients with bladder cancer is whether earlier detection is possible. However, early diagnosis of bladder cancer remains a clinical challenge (3). Currently, the reference standard of diagnosis and detection of bladder tumors is histopathology, but it is an invasive and relatively costly technique, and, occasionally, inconclusive, while conventional imaging tests, such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) have significant limitations in determining the stage of bladder cancer, particularly for superficial lesions (4). Thus, a real-time, improved tool is urgently required for detecting early bladder cancer patients.

Optical coherence tomography (OCT) is a type of biomedical optical imaging technique and optical biopsy that was first introduced in 1991 (5). Unlike conventional histopathology, OCT may function as 'optical biopsy' and is analogous to ultrasound providing real-time and cross-sectional images of tissue structure at a resolution of ~10 μm, which is similar to that of histopathology (6). OCT was initially applied for quantitative assessment of retinal structures in patients with macular edema (7). Subsequently, this approach was used in a wide spectrum of clinical applications, including human coronary arteries, structure of the digestive system, cervical epithelium and urinary tissues (6,8-10). These studies considered OCT to be a successful optical imaging modality (11). Recent studies suggest that OCT is used to help diagnose bladder cancer or to detect recurrence in patients who have already been treated, and this approach may be helpful with staging and grading of bladder cancer (12,13). The present meta-analysis was performed to assess the diagnostic performance of OCT in patients with bladder cancer and recurrent lesions using histopathology as the golden standard.

Data collection methods

Search strategy and selection criteria. The PubMed, EMBASE and Cochrane Library databases were searched for studies using OCT in patients with bladder cancer between January 1991 and December 2014. The searches were performed using the terms 'optical coherence tomography', 'OCT', 'optical

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Key words: bladder cancer, optical coherence tomography, meta-analysis, diagnostic accuracy

biopsy', 'bladder cancer', 'transitional cell carcinoma' and 'urothelial carcinoma'. Studies were included if they compared OCT with the gold standard (histopathology/cytology) in the diagnosis of patients with bladder cancer, and reported data such as sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN). Studies were excluded if they were reviews, laboratory articles or case reports, if they were not published in English, if there was duplication of data, or if they did not provide detailed data to perform a meta-analysis.

Study selection and data extraction. The eligible studies were assessed by two independent reviewers (J Huang and XL Ma). Disagreements on study selection or data extraction were resolved by consensus or by discussion with a third reviewer (L Liu). The data were extracted from eligible studies using a standardized data collection form, including related items: First author, publication year, number of patients, patient source, study design, patient age, reference standard for the diagnosis and other useful information. TP, FP, TN and FN were eventually acquired/calculated to perform the meta-analysis.

Quality assessment. Quality assessment was independently performed by two investigators (J Huang and XL Ma) using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS) (14). Briefly, this tool assesses diagnostic trials and contains 14 questions. Each item was assessed as 'yes', 'no' or 'unclear'. Any discrepancies were resolved by consensus.

Data analysis/statistical analysis. The present meta-analysis was performed to assess the accuracy of OCT in patients with bladder cancer. The pooled estimates were determined by the fixed-effects model (Mantel-Haenszel method) if significant heterogeneity was not detected, whereas the random-effects model (DerSimonian-Laird method) was applied if there was heterogeneity between studies. The χ^2 test and I^2 statistic were applied to assess heterogeneity: $P<0.05$ for the χ^2 test and $I^2>50\%$ were considered to indicate heterogeneity between studies. The summary Receiver Operating Characteristic (sROC) approach was a type of standard method applied in the evaluation of diagnostic technologies of diagnostic accuracy studies reporting pairs of sensitivity and specificity. The Q-point is the point on the sROC curve where sensitivity equals specificity (15). The area under the curve (AUC) was applied to assess the quality of the diagnostic tool, which is defined as perfect when the AUC is 100% (16). The data including TP, FP, TN, FN were acquired using RevMan 5.1 software (Cochrane Collaboration, Oxford, UK). The pooled estimates [sensitivity, specificity, positive likelihood ratio (LR), negative LR and diagnostic odd ratio (OR)] were calculated using Meta-Disc software, version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).

Assessment of publication bias. Begg's test and funnel plots were used to determine potential publication bias using STATA 11.0 software (STATA Corporation, College Station, TX, USA), and $P>0.05$ was not considered as potential publication bias.

Results

Eligible studies. The electronic search through PubMed, EMBASE and the Cochrane Library identified 73 publications. After screening the titles and abstracts, 45 studies were considered for further evaluation. Of the 45 studies, only 9 met the inclusion criteria and were considered suitable for inclusion in the meta-analysis for OCT and bladder cancer (Fig. 1) (4,17-24). All the eligible studies were published between 2002 and 2014. A total of 468 patients were included in these studies (range, 20-105 patients). The clinical characteristics of the patients and other useful information, such as authors, country and tumor stage, are summarized in Table I.

Quality assessment. Quality assessment was performed in all the included studies using the QUADAS tool (Table II). Of the 14 items, at least 10 items were clearly stated in each eligible study, which indicates high quality.

Diagnostic accuracy of OCT in bladder cancer. The forest plot of sensitivity and specificity for diagnostic accuracy of OCT in bladder cancer patients is presented in Fig. 2. The sensitivity of the eligible studies ranged from 0.76 to 1.00, and the specificity ranged from 0.62 to 0.97. The pooled sensitivity and specificity with 95% confidence interval (95% CI) for OCT were 0.96 (95% CI: 0.94-0.98) and 0.82 (95% CI: 0.80-0.85), respectively. The pooled PLRs and NLRs were 6.83 (95% CI: 3.24-14.1) and 0.05 (95% CI: 0.02-0.16), respectively. The combined diagnostic odds ratio (DOR) in the diagnosis of bladder cancer was 138.88 (95% CI: 29.63-650.89). The pooled values (sensitivity, specificity, PLR, NLR and DOR) are listed in Table III. The sROC and the Q^* index were used to assess diagnostic accuracy. The AUC and the Q^* index were 0.9735 and 0.9257, respectively.

Study heterogeneity and publication bias. Heterogeneity was assessed on the basis of the χ^2 test and the I^2 statistic. There was statistically significant heterogeneity in sensitivity ($\chi^2=26.12$, $P=0.0010$; $I^2=69.4\%$), specificity ($\chi^2=109.09$, $P=0.0000$; $I^2=92.7\%$), positive LR ($\chi^2=154.93$, $P=0.0000$; $I^2=94.8\%$), negative LR ($\chi^2=35.40$, $P=0.0000$; $I^2=77.4\%$) and DOR ($\chi^2=49.94$, $P=0.0000$; $I^2=84.0\%$). Publication bias was analyzed by Begg's test and funnel plots. No significant publication bias was found for DOR in the present meta-analysis ($P=0.83$).

Discussion

Bladder cancer is the sixth most common type of cancer worldwide. Approximately 75-85% of patients have superficial bladder cancer when first diagnosed, confined to the mucosa or lamina propria. However, a significant proportion of patients with superficial bladder cancer are at risk for recurrence and progression. The risk factors for tumor recurrence and/or progression may be summarized as follows: i) New tumor occurrence and progression; ii) tumor implantation during transurethral resection (TUR); iii) residual tumor following incomplete resection and/or iv) overlooking of neoplastic lesions such as dysplasia and carcinoma *in situ* (CIS) (25). Tumor recurrence and/or progression are partially attributed

Table I. Characteristics of the eligible studies.

Authors	Year	Origin	Study design	Patient no. (M/F)	Age (range or mean, years)	Tumor stage	Analysis method	(Refs.)
Goh and Lerner	2008	USA	Retro	32 (25/7)	59 (49,84)	Ta, T1, T2	OCT	(12)
Gladkova *et al*	2013	Russia	NR	26 (18/8)	64.7 (3479)	CIS, Ta, T1, T2	Cross-polarization OCT	(22)
Wang *et al*	2006	USA	Retro	>20	NR	T1, T2a	OCT	(23)
Schmidbauer *et al*	2009	Austria	Prosp	66 (49/17)	67 (38-84)	CIS, Ta, T1, T2	OCT	(20)
Ren *et al*	2009	USA	NR	56 (46/10)	70 (25-75)	pTis and pTa-pT1	Cystoscopic OCT	(19)
Manyak *et al*	2005	USA	NR	24	NR	Papillary and flat lesions	OCT	(4)
Lingley-Papadopoulos *et al*	2009	USA	NR	21	NR	CIS, papillary lesion, or invasive tumor	OCT	(24)
Karl *et al*	2010	Germany	NR	52	21-91	CIS, Ta, T1, T2	OCT	(18)
Hermes *et al*	2008	Germany	Retro	105	NR	CIS, invasive carcinoma	Ultrahigh resolution OCT	(17)

Ta, Tis and T1 are classed as superficial bladder cancers. Prosp, prospective; Retro, retrospective; M, male; F, female; NR, not reported; CIS, carcinoma *in situ*; Ta, Tis, tumors confined to the mucosa; T1, submucosa; T2, muscle-invasive bladder cancer; OCT, optical coherence tomography.

Figure 1. Flow diagram of the study selection process.

to the detection tools. Therefore, new diagnostic modalities for detection and monitoring are required to decrease the rate of tumor recurrence and/or progression, which affect the patient outcome.

Accumulated evidence indicates that current methods of diagnosing bladder cancer mainly rely on histological and cytological examination of tissue. White-light cystoscopy in combination with TUR are currently applied to resect lesions, followed by histopathological examination to evaluate the level of bladder wall involvement. Histopathological examination is currently the gold standard for identifying bladder cancer tissue. This pathological examination is a time-consuming procedure that requires removal of suspicious lesions, followed by fixing and staining prior to diagnosis. Furthermore, histopathological evaluation in the diagnosis of bladder cancer has certain limitations in terms of real-time differentiation of grade and stage of superficial bladder cancer, since relevant early-stage and precancerous lesions are often missed (26-28). Cystoscopic evaluation is available for papillary transitional cell carcinoma (TCC); however, it is of low diagnostic sensitivity and specificity for differentiating non-papillary TCC, particularly CIS (29-31). Urine cytology has been proven to have potential advantages for bladder CIS and high-grade neoplasms, but is of quite low sensitivity for low-grade lesions and follow-up investigations of bladder cancer (32). The abovementioned methods are invasive detection techniques that remain insufficiently validated in terms of diagnosis and follow-up, particularly for low-grade bladder cancer. In addition, as regards non-invasive detection tools, due to the limited resolution, conventional imaging tools, including intravenous pyelography, CT and MRI, fail to detect early-stage bladder cancer (3). Furthermore, real-time grading of bladder cancer is clinically important, but the previously mentioned approaches for diagnosis and grading cannot provide this information. Thus, a new, real-time, promising detection method is needed to enable accurate diagnosis for superficial bladder cancer and recurrent disease.

OCT as a real-time high-resolution and non-invasive technology, may provide cross-sectional imaging of biological tissue to a depth of 1-2 mm (33). This tool may increase accuracy and specificity in differentiating grade and stage in bladder cancerous lesions in particular, offering great potential for the detection of precancerous and low-grade lesions,

Table II. Quality assessment of included studies.

Item	Studies (Refs.)								
	Goh and Lerner (12)	Ren *et al* (19)	Hermes *et al* (17)	Manyak *et al* (4)	Gladkova *et al* (22)	Karl *et al* (18)	Wang *et al* (23)	Schmidbauer *et al* (20)	Lingley-Papadopoulos *et al* (24)
1	Y	N	Y	Y	N	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	N	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	N	Y	N	N	Y	Y
10	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	Y	U	Y	Y	Y	Y	Y	N	Y
14	Y	U	Y	Y	Y	Y	U	N	Y

QUADAS criteria
1. Was the spectrum of patients' representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to correctly classify the target condition?
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard or diagnosis?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterpretable/intermediate results reported?
14. Were withdrawals from the study explained?

Y, yes; N, no; U, unclear; QUADAS, Quality Assessment Tool for Diagnostic Accuracy Studies.

Table III. Diagnostic accuracy of OCT in bladder cancer in 9 selected studies.

Data analysis	Pooled value	95% confidence interval
Sensitivity	0.96	0.94-0.98
Specificity	0.82	0.80-0.85
PLR	6.83	3.24-14.41
NLR	0.05	0.02-0.16
DOR	138.88	29.63-650.89

OCT, optical coherence tomography; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

and may also be available for visualization and resection. To date, OCT has been widely applied to diagnose patients suffering from bladder cancer. Hermes *et al*, as well as other groups, demonstrated that OCT is a clinically useful tool for bladder cancer diagnosis with high sensitivity and specificity (13,17). Johnson *et al* demonstrated the feasibility of OCT in the diagnosis of glaucoma by a systematic review and meta-analysis (34). OCT diagnostic technologies for bladder cancer have not been compared with histopathology examination by meta-analysis to date.

To the best of our knowledge, this is the first meta-analysis investigating the diagnostic accuracy of emerging OCT in bladder cancer. Histopathology served as the reference standard. A total of 9 eligible studies (468 patients) were included in our meta-analysis, and the pooled estimated sensitivity and specificity of OCT in detecting bladder cancer were 0.96 (95% CI: 0.94-0.98) and 0.82 (95% CI: 0.80-0.85), respectively. As seen in Table I, the included patients were mainly low-grade and early-stage (superficial bladder cancer and CIS). The results of the present meta-analysis suggested that

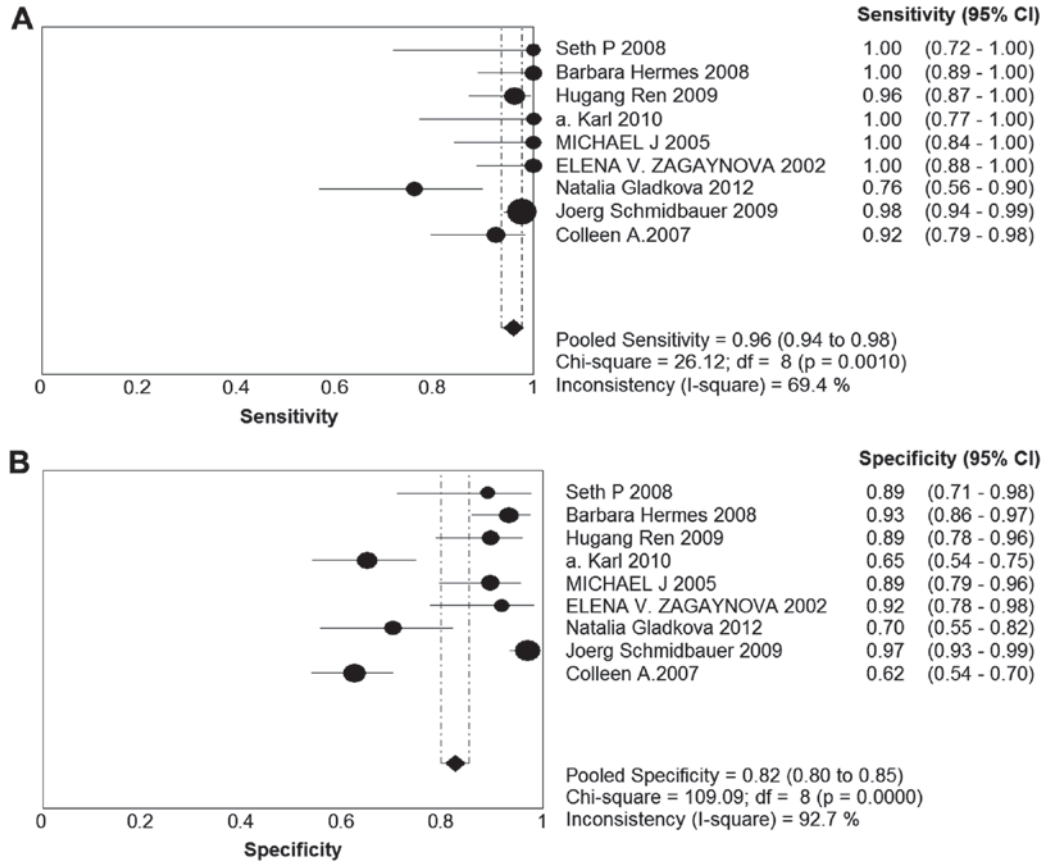

Figure 2. Forest plot of sensitivity and specificity of optical coherence tomography in the diagnosis of patients with bladder cancer. CI, confidence interval.

OCT has excellent diagnostic performance for low-grade and early-stage disease in bladder cancer patients.

In this study, the OCT signal was assessed *per se*, as well as in combination with other imaging modalities, such as fluorescence spectroscopy. The results revealed that there was no significant difference in the diagnostic value (data not shown). The factors limiting the validity of the results are summarized as follows: i) The eligible studies mainly analyzed the diagnostic role of OCT in early-stage bladder cancer patients; and ii) there was not enough evidence for further analysis.

DOR is a single indicator of diagnostic accuracy that combines the data into a number (9); it ranges from 0 to infinity, and higher values indicate higher accuracy. Although there is no absolute cut-off, a good diagnostic test must have a DOR of >100. The pooled DOR value for OCT was 138.88 (95% CI: 29.63-650.89) in the present meta-analysis. AUC was also applied to determine the diagnostic accuracy. The value of AUC was 97.35% in the diagnosis of bladder cancer. Taken together, these results indicate that OCT, a real-time high-resolution and non-invasive technique, has a very high level of accuracy.

There were several limitations in our studies. The major limitation of OCT are its innate characteristics. OCT functions as an 'optical biopsy' and is equivalent to ultrasound based on depth-resolved detection of elastic light scattering. The imaging depth is usually limited to <2 mm due to light scattering by the sample. Therefore, OCT has the potential to differentiate grade and stage of early bladder cancer, but is less useful for advanced tumors. Combining OCT with other imaging modalities, such as fluorescence spectroscopy or advanced analysis of the OCT signal itself, may distinguish between benign and malignant bladder tissue, regardless of disease stage. Another limitation of OCT is the difficulty in differentiating between chronic inflammatory tissue and CIS, which is also the case for edema and scar tissue. In addition, the numbers of the patients in the eligible studies were small, and the majority had low-grade (non-invasive) bladder cancer and CIS, which may have introduced a bias to the results. Therefore, a study including a larger population is required to assess the accuracy of OCT. Selective reporting biases are one of common risks with diagnostic studies. At present, the results appear to be in favor of OCT. In addition, the exclusion of studies, regardless of the reason, may have also led to potential reporting bias. It is also noteworthy that this clinical diagnostic tool has not been widely adopted and there are no consolidated guidelines regarding imaging for bladder cancer.

Significant heterogeneity was found in the present meta-analysis. The heterogeneity in sensitivity, specificity, positive LR, negative LR and DOR were χ^2=26.12, P=0.0010, I^2=69.4%; χ^2=109.09, P=0.0000, I^2=92.7%; χ^2=154.93, P=0.0000, I^2=94.8%; χ^2=35.40, P=0.0000, I^2=77.4%; and χ^2=49.94, P=0.0000, I^2=84.0%, respectively. This indicated that there were significant variations in the studies, such as the examiner's experience, analysis imaging using the OCT signal *per se* or combining OCT with other imaging modalities, number of patients or detected lesions and study design. In addition, Begg's test is likely underpowered due to the small number of studies and the high heterogeneity.

The meta-analysis indicated that OCT may be a useful and promising tool for earlier detection, diagnosis and staging of superficial low-grade tumors and CIS, as well as detection of recurrent tumors. Since real-time high-resolution OCT images may be obtained in a non-invasive manner, it would play an important role in guided therapies. In particular, this tool may prove useful for guidance of biopsy procedures and staging of suspected tissue areas within the bladder. However, multicenter and prospective studies are required to provide definitive answers and evaluate the potential diagnostic accuracy of OCT in the detection of early bladder cancer.

Acknowledgements

The present study was supported by the National Natural Science Foundation of China (grant no. NSFC 81101729) and the Soft Science Project of Sichuan Province (grant no. 2010ZR0161).

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