Optical Coherence Tomography in Urologic Oncology: a Comprehensive Review

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Abstract

Introduction Optical coherence tomography (OCT) is being investigated in urologic oncology for optical diagnosis. This comprehensive review analyzes the current state of development of OCT for bladder, upper urinary tract, kidney, prostate, testis, and penis cancer. Also, the potential role of OCT with regard to the current diagnostic pathways is critically appraised to guide future developments. **Methods** Embase and Pubmed were systematically searched for English and German articles on OCT in humans up to December 2017. Reviews were excluded. Case reports were excluded, unless they presented a landmark in the development of OCT. **Results** Out of 878 articles, 17 relevant articles on bladder, seven on kidney, five on upper urinary tract, four on prostate, and two on penile cancer were included. In these organs, in vivo OCT imaging is feasible with potential for qualitative and quantitative diagnosis, grading and staging in specific organs. The development of OCT has reached IDEAL stage 2b with 2b level of evidence. Relevant articles on testis cancer were lacking.

Conclusion OCT allows for non- or minimally invasive cancer diagnosis in the bladder, upper urinary tract, kidney, prostate, and penis. In some organs, OCT also may enable histologic grade and stage prediction. However, the current evidence is still at an exploratory level. With regard to the potential additional value of OCT in comparison to the current diagnostic pathways, OCT could become a diagnostic replacement or add-on test for urothelial carcinoma, penile carcinoma, and renal masses. Further research in these conditions should be encouraged.

Keywords Optical coherence tomography · Urothelial carcinoma · Prostate carcinoma · Kidney cancer · Penile carcinoma · Testis carcinoma

Introduction

In quest of optimizing diagnostic pathways, new imaging modalities are constantly developed. Among them, optical

imaging is riding on the crest of a wave with a good example on the rising interest in optical coherence tomography (OCT).

OCT, also called the optical analogue of ultrasound imaging, facilitates in vivo high-resolution cross-sectional imaging of tissues. In contrast to ultrasound imaging, which uses time of flight measurements for depth ranging, OCT depth information is obtained by low-coherence interferometry, in which the depth resolution is determined by the coherence length of the broadband light source. The contrast in the OCT depth scans is based on differences in backscattering properties of the tissue under study. These contrast-based reflection profiles are called amplitude scans (A-scans). As the amplitude of the backscattered light is related to tissue-specific optical properties, tissue-distinctive A-scans are yielded. Adjacent A-scans can be merged to create two-dimensional scale cross-sectional OCT brightness scans (B-scans), (Fig. 1). Based on these B-scans, OCT systems can generate three-dimensional image sets for improved spatial insight.

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From A-scan to B-scan to 3D-scan

Fig. 1 From amplitude scan to brightness scan to 3D scan. Legend: **a** amplitude scan of OCT, **b** brightness scan of OCT, **c** three-dimensional scan of OCT

In general, OCT systems that utilize near-infrared light have an axial resolution of $\sim 10 \mu\text{m}$. Therewith, OCT fills the gap on the resolution scale between confocal microscopy and ultrasound imaging. The amplitude of the backscattered light reduces exponentially with tissue depth. This limits the OCT imaging range to approximately 2–3 mm tissue depth.

At present, OCT has become a valuable tool for non- or minimally invasive imaging in ophthalmology and cardiology due to its non-contact mode imaging capabilities and image resolution. OCT seems also ideal for imaging of epithelial tumors as most of them arise within the first millimeters of the superficial layers [1]. Furthermore, carcinogenesis alters the nuclear morphology, which changes the optical properties of malignant tissue. This leads to differences in OCT reflection profiles between benign and malignant tissue [2]. Hence, these OCT reflection profiles allow for qualitative and quantitative assessment for tumor diagnosis. Tissue layers can be delineated visually on OCT B-scans. Also, quantitative analyses of OCT images have been explored. Statistical, structural, and spectral texture analyses of OCT images have been applied for computer-aided tumor detection [3, 4]. Quantification of OCT signal depolarization may also serve for automated diagnosis [5, 6]. Furthermore, the decrease in OCT signal with tissue depth, quantified by the attenuation coefficient (μ_{OCT} , mm^{-1}), has been explored for cancer diagnosis and histologic grading [7–9].

Currently, three different types of devices, interfaced to OCT systems, have been investigated for urologic applications: (1) handheld forward-looking devices, (2) forward-looking probes of $> 3 \text{ Fr}$, and (3) sideward-looking probes of $< 3 \text{ Fr}$. The handheld device is used for extracorporeal en face OCT imaging of epithelial tissue. Forward-looking probes are used for en face OCT imaging of tissue during endoscopic or laparoscopic procedures. Sideward-looking probes, developed for cardiovascular imaging, are compatible with flexible ureteroscopes and 18-G needles, and hence enable

ureterorenoscopic or needle-based imaging of soft tissues. Characteristic for the sideward-looking probes is the automated rotary pullback system that enables helical imaging of the peripheral surrounding during the pullback. The availability of different types of OCT devices and the variety in OCT image assessment methods facilitate possibilities to optimize the current diagnostic pathways in urologic oncology.

The aim of this comprehensive review is to provide an overview of the current state of development of OCT in urologic oncology. Secondly, the diagnostic and clinical practical value of OCT for the diagnosis of malignancies in the bladder, upper urinary tract, kidneys, prostate, testis, and penis are discussed. The assessment of the current state of development and the potential role of OCT is essential to guide further developments towards clinical implementation into urologic oncology.

Materials and Methods

A systematic search of the literature was conducted in PubMed and Embase for each urologic cancer with key terms to identify English and German original articles on OCT in human studies until December 2017 (Appendix A). All original articles on ex vivo or in vivo human studies were included. Animal studies were excluded. In case of overlapping study populations from the same group, only the most recent article was included. Reviews were excluded. Case reports were also excluded, unless the findings presented a landmark in the development of OCT.

Data extraction was performed by two independent reviewers (J.F., D.d.B.). In case of disagreement, consensus was reached with a third reviewer (M.B.). The results of the evidence acquisition are illustrated in Appendix A.

Table 1 Overview of key considerations used to determine the “Idea, Development, Exploration, Assessment and Long-term follow-up (IDEAL) stages” as reported by Pennell et al. in the British Journal of Surgery in 2016

IDEAL stage	Characteristics of reports	Key issues addressed and content items	Key milestones for stage completion
Idea (1)	One or very few reports. Only case reports or very small case series.	States that this is the first in humans. Detailed technical description.	Reports an intervention not previously used in humans.
Development (2a)	Small number of reports. Reports from one or a few centers. All reports have small number of patients	Safety of procedure. Short-term outcomes. Discusses indications and technical detail and may describe modifications.	Content and nature of reports suggest that intervention technique has reached stability.
Exploration (2b)	Increasing number of reports, patients per report, and centers involved. Some prospective collaborative studies (registries, audits, databases).	Discusses procedural quality and learning curves. Comparison of outcomes with standard treatment. Calls for an RCT to be done.	Reports suggest that consensus has been reached on optimal technique, indications, and outcome measures.
Assessment (3)	Reports of multicenter RCTs. Quasi-experimental designs. Stepped-wedge designs. Case-matching studies. Analysis of large data sets with risk adjustment.	Compares procedure with standard treatment.	Reports document a high-quality RCT or other valid experimental comparison of the intervention compared with the current standard of care.
Long-term (4)	Long-term cohort studies. Retrospective case series. Registries and databases.	Reports long-term outcomes. Identifies rare outcomes. May analyze risk or prognostic factors. May report on changing indications.	Ongoing reports of late or rare outcomes, which patients benefit most, whether indications are changing, variation in performance

The level of evidence (LoE) of the included articles was assessed according to the Oxford Centre for Evidence-based Medicine model [10]. Furthermore, the articles were rated according to the IDEAL recommendations to assess the current state of development [11]. Table 1 illustrates the key considerations to determine the IDEAL stage as reported by Pennell et al. [11].

We did not proceed to a systematic review because of the explorative stage of OCT in urology.

Results

Bladder Cancer

Bladder cancer (BC) is ranked among the ten most common cancers worldwide [12]. BC arises in 90% of the cases from the urothelium. Normal urothelium consists of a well-organized layer of 2–7 transitional cells with a mean layer thickness of 61 μm [13]. The urothelium is demarcated from the underlying lamina propria (LP) by the basement membrane. Underneath the LP lies the muscularis propria (MP). In a normal condition, all tissue layers of the bladder are regularly structured and well organized [14, 15]. Malignant urothelium, however, has a tendency towards disorganization of the microarchitecture and the possibility of invasiveness into the underlying tissue layers.

Histopathological assessment of BC is fundamental for diagnosis, risk-stratification, and prognosis. However, the clinical practical value and the diagnostic accuracy of transurethral biopsies or resection are limited [16]. Especially, the identification of carcinoma in situ (CIS) is challenging with white light cystoscopy [12]. Furthermore, in the absence of transurethral resection or biopsies, the diagnostic pathway for BC lacks histologic certitude for a definite diagnosis. This hampers direct outpatient treatment of low-risk tumors with active surveillance or laser fulguration. Therefore, new optical imaging techniques such as OCT may lead to an improvement of the current diagnostic pathway and personalized care for BC.

Twenty relevant articles on OCT in BC were identified in the systematic search, of which two were overlapping study populations (Table 2) [1, 3, 5–7, 17–29].

OCT imaging of human urologic tissue was performed for the first time in an ex vivo setting in 1997 [25]. Shortly thereafter, the first in vivo OCT imaging was performed during cystoscopy with a forward-looking OCT probe. Visual delineation of tissue layers with OCT was feasible. The size of the cellular structures on OCT images corresponded with histologic morphometry of the resection specimen [1]. Further studies reaffirmed the following OCT characteristics of bladder tissue: normal urothelium is seen as a thin horizontal layer of uniform low signal intensity [6, 17, 21, 22, 26–29]. The LP

Table 2 Overview of studies on OCT for human bladder cancer

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE	IDEAL stage
Kiseleva et al., 2017	Prospective cohort, ex vivo	Assessing CP OCT for BC	18 (60)	CP OCT, AR na, 1310 nm λ	Cystectomy specimen	In mild inflammation, the urothelium is visualized as a continuous layer of high CP OCT signal intensity, while in severe inflammation, the OCT signal intensity is lower. In poorly differentiated invasive BC, the urothelium is structureless with low OCT signal intensity.	Depolarization factor maps and integral depolarization factor analysis enabled differentiation of BC from inflammation.	3b	2a
Kiseleva et al., 2015	Prospective cohort, in vivo	Assessing computer-aided CP OCT analysis for BC	73 (96)	CP OCT 1300 U, 8 Fr FL probe, 20 μ m AR, 1315 nm λ	Biopsy	NP	Computer-aided integral depolarization factor analysis enabled differentiation of BC from inflammation with a diagnostic accuracy was 75%. Also recurrence in the post-operative scar could be identified with this technique in 97% of the cases.	2b	2b
Gladkova et al., 2013	Prospective cohort, in vivo	Assessing CP OCT in comparison to OCT and fluorescence cystoscopy	26 (92)	CP OCT 1300-U, 8 Fr FL probe, 15 μ m AR, 1315 nm λ	Biopsy	Visual assessment of traditional and CP OCT images as an add-on to fluorescence cystoscopy improved the diagnostic accuracy for CIS diagnosis. The best results were reached with CP OCT as an add-on, resulting in a sensitivity of 90% and a specificity of 92% for CIS.	The quantitative estimation of the CP OCT signal intensity, expressed as standard deviations in dB, differed significantly in benign states from CIS and BC. A value of 4.32 dB was taken to be the threshold for diagnosing CIS. This yielded a sensitivity of 96% with a specificity of 92% for CIS detection in combination with fluorescence cystoscopy.	2b	2a
Gladkova et al., 2011	Prospective cohort, in vivo	Comparing traditional OCT with CP OCT for BC diagnosis	116 (360)	CP OCT, 8 Fr FL probe, 15 μ m AR, 1300 nm λ	Biopsy	CP OCT image assessment leads to a sensitivity of 94% and a specificity of 84% in detecting CIS. Visual interpretation of traditional OCT images resulted in a significantly lower sensitivity (81%) and specificity (70%).	NP	2b	2b
Cauberg et al., 2010	Prospective cohort, ex vivo	Assessing μ OCT analysis for BC grading	18 (54)	Time domain OCT, 14 μ m AR, 850 nm λ	Resection chips	NP	μ OCT analysis did not predict BC tumor grade. The median μ OCT of benign tissue was 5.75 mm ⁻¹ vs 5.52 mm ⁻¹ , 4.85 mm ⁻¹ , and 5.62 mm ⁻¹ for grade 1, 2, and 3 BC, respectively.	2b	2a
Karl et al., 2010	Prospective cohort, in vivo	Assessment of OCT for BC diagnosis	52 (102)	Niris OCT, 8 Fr FL probe, 20 μ m AR, 1310 nm λ	Biopsy or resection chips	Sensitivity and specificity for visual BC diagnosis with OCT were 100% and 65% respectively. The sensitivity for detection of tumor growth beyond the lamina propria was 100%.	NP	2b	3
Schmidbauer et al., 2009	Prospective cohort, in vivo	Assessment of OCT adjunct to WL or fluorescence cystoscopy	66 (232)	Niris OCT, 8 Fr FL probe, 15 μ m AR, 1310 nm λ	Biopsy	Combining fluorescence cystoscopy with targeted OCT increased the specificity significantly. Sensitivity and specificity for BC detection with WL cystoscopy were 69.3% and 83.7%, with fluorescence	NP	2b	3

Table 2 (continued)

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE	IDEAL stage
Ren et al., 2009	Prospective cohort, in vivo	Assessment of OCT for BC diagnosis	56 (110)	Spectral-domain OCT, 8 Fr FL probe, 10 μ m AR, 1320 nm λ	Biopsy or resection chips	cystoscopy 97.5% and 78.6% and with fluorescence cystoscopy adjunct to targeted OCT 97.5% and 97.9%. Sensitivity of OCT for BC detection was significantly higher (94%) than cystoscopy alone (75%) and voided cytology (59%). Specificity of OCT (81%) was comparable to voided cytology (88.9%), but significantly higher than that for cystoscopy (62.5%). OCT enabled correct staging in 18/20 Ta BC.	NP	2b	3
Goh et al., 2008	Prospective cohort, in vivo	Assessment of OCT for intraoperative BC staging	32 (38)	Niris OCT, 8 Fr FL probe, 15 μ m AR, 1310 nm λ	Biopsy or resection chips	OCT enabled correct identification of invasion into the lamina propria in 11/11 $\geq$ T1 BC. OCT enabled correct staging in 7/7 MIBC.	NP	2b	3
Lingley-Papadopoulos et al., 2009	Post-hoc analysis of two prospective cohorts, in vivo	Evaluation of two texture analysis algorithms for OCT-based cancer detection	Training set: 22 (196) Test set: 34 (96)	Imalux Corporation OCT, 8 Fr FL probe, AR na, test set 1310 nm λ , training set 980 nm λ	Biopsy	NP	With images from the same OCT system, the OCT system dependent algorithm for texture analysis yielded a sensitivity of 73% and a specificity of 69% for BC, but the algorithm failed with images from a different OCT system. Regardless of the OCT system, the OCT system independent algorithm for texture analysis demonstrated a sensitivity of 87% and a specificity of 58% for BC diagnosis.	2b	2b
Hermes et al., 2008	Prospective cohort, ex vivo	Defining OCT parameters for BC diagnosis	na (142)	Sirius 713 OCT, FL probe, 3 μ m AR, 800 nm λ	Resection chips, cystectomy	The basement membrane was identified as a continuous layer of minimum signal intensity between the urothelium and lamina propria in normal urothelium and non-invasive BC. This membrane allows for reliable exclusion of tumor invasion. Visual assessment of OCT yielded a sensitivity of 83% and a specificity of 78% for BC diagnosis.	NP	2b	2a
Sengottayan et al., 2008	Prospective cohort, in vivo	Evaluation of intraoperative BC staging with OCT	32 (38)	Niris OCT, 8 Fr FL probe, 15 μ m AR, 1310 nm λ	Biopsy or resection chips	OCT-based staging of Ta BC yielded a sensitivity of 90% and a specificity of 89%. In T1 BC, OCT-based staging yielded a sensitivity of 75% and a specificity of 97%. In MIBC, OCT-based staging resulted in a sensitivity of 100% and a specificity of 90%.	NP	2b	2b
Danilchenko et al., 2006	Prospective cohort, in vivo	Defining OCT parameters for BC diagnosis	50 (326)	Sirius 713 OCT, FL probe, AR na, 1300 nm λ	Biopsy or resection chips	Inflammatory urothelium is depicted by a continuous, thickened layer of reduced signal intensity with blurring of stratification. Ta BC is characterized by a	NP	2b	2a

Table 2 (continued)

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE	IDEAL stage
Manyak et al., 2005	Prospective cohort, in vivo	Assessment of OCT for visualization of epithelial and subepithelial anatomic structures	24 (87)	Imalux Corporation OCT, 8 Fr FL probe, 10–20 μ m AR, 980 nm λ	Biopsy	thickened, irregular but continuous layer of increased signal intensity. MIBC is characterized by loss of stratification and heterogeneous OCT signal. Benign bladder tissue is characterized by three stratified layers: U of uniform thickness, LP as a bright, thin continuous layer, and MP as a darker layer. NMIBC is visualized as stratified layers but with low contrast between the U and LP, where the continuous LP is poorly defined or with focal disorganization. MIBC appeared as disorganized U with disrupted LP and poor differentiation between layers. Sensitivity and specificity for BC diagnosis were 100% and 89%.	NP	2b	2a
Zagaynova et al., 2008	Prospective cohort, in vivo	Assessing flat lesions with OCT and OCT-guided TURB	80 (114)	OCT, 8 Fr FL probe, AR na, 1300 nm λ	Biopsy or resection chips	OCT yielded a sensitivity of 85% and a specificity of 68% for the diagnosis of CIS. 79% of false positive fluorescent lesions showed typical benign OCT images. OCT-based assessment of the resection line yielded a sensitivity of 93% and a specificity of 74% for the identification of irradical resection margins.	NP	2b	2a
Jesser et al., 1999	Case series, ex vivo	Feasibility study of OCT for BC	8 (na)	AFC OCT, 18 μ m AR, 1310 nm λ	Autopsy or resection chips	OCT of normal bladder tissue enabled delineation of tissue layers: mucosa, submucosa, and muscle layers. In MIBC, the delineation of tissue layers was not possible.	NP	4	1
Sergeev et al., 1997	Case series, in vivo	Feasibility study of endoscopic OCT	3 (na)	OCT, 8 Fr FL probe, AR na, 830 nm λ	Resection	Visual tissue layer identification of the urothelium, LP, and muscle was feasible. The sizes of cellular structures in OCT images were in concordance with sizes in resection specimen.	NP	4	1
Tearney et al., 1997	Case series, ex vivo	Feasibility study of endoscopic OCT	5 (na)	OCT, 16 μ m AR, 1300 nm λ	Autopsy	Visual identification of the mucosa, submucosa, and muscularis propria of the bladder. Muscular layers had a higher OCT signal intensity than mucosal and adventitial layers.	NP	5	1

λ , wavelength; μ OC7, attenuation coefficient; AR, axial resolution; BC, bladder cancer; CIS, carcinoma in situ; CP, cross-polarization; FL, forward-looking; IDF, integral depolarization factor; LoE, level of evidence; LP, lamina propria; MIBC, muscle-invasive bladder cancer; na, not available; NMIBC, non-muscle-invasive bladder cancer; NP, not performed; OCT, optical coherence tomography; ROI, region of interest; U, urothelium; WL, white light

causes more scattering and thus appears as a brighter horizontal underlying layer with OCT. Due to the abrupt change of optical properties between the urothelium and the LP, a clear demarcation between the tissue layers can be seen in OCT images (Fig. 2). Between these two layers, the basement membrane may be visualized with OCT, enhancing the demarcation between the urothelium and the LP. Interruption of this demarcation line in OCT images is a characteristic for tumor invasion (Fig. 2) [21, 28]. In OCT images of muscle-invasive BC, the layer of the LP is irregular or disrupted towards the MP [17, 21, 26, 27]. Regardless of invasiveness, BC is usually visible as an irregular, thickened layer of heterogeneous signal intensity in OCT images. The visualization of CIS by means of OCT is difficult. In OCT images, CIS and inflammation are characterized by heterogeneous signal intensity of the unbroadened urothelium, causing a reduced contrast with the untouched LP [27].

Several studies have described the use of OCT as adjunct to white light cystoscopy for bladder cancer diagnosis and staging [17, 20, 26, 27, 29]. In these mainly small cohorts, the sensitivity and specificity of OCT during cystoscopy for BC diagnosis ranged from 75 to 100% and 65 to 89%, respectively [6, 17, 21, 22, 26]. OCT adjunct to cystoscopy resulted in an increase in sensitivity and specificity of 19% for BC diagnosis in comparison to WL cystoscopy [19]. Schmidbauer et al. and Zagaynova et al. also illustrated an increase in the diagnostic accuracy when using OCT in conjunction with photodynamic diagnostics [17, 20]. For the diagnosis of non-muscle-invasive BC, Goh et al. reported a sensitivity of 75–90% and a specificity of 89% with OCT. For the diagnosis of BC invasion,

sensitivities of 100% and a specificity of 77–90% were reported for OCT [17, 29].

Besides qualitative assessment, quantitative analysis of changes in OCT cross-polarization backscattering and integral depolarization factor reached a diagnostic accuracy for BC of 75% [5, 6, 23]. However, quantitative analysis of the μ_{OCT} was not feasible in ex vivo for BC diagnosis and grading. The negative results were thought to be caused by the ex vivo study design [7].

In summary, OCT enables qualitative BC diagnosis and staging but the current state of development is at IDEAL stage 2b with evidence limited to level 2b. Cross-polarization OCT may enable quantitative BC diagnosis and other quantitative OCT-based analyses should be explored further. As such, OCT could facilitate a real-time outpatient evaluation of suspicious bladder lesions without transurethral resection for histopathology. However, qualitative OCT-based diagnosis of CIS was not possible due to the similarity with inflammation. Future research should be stimulated to reaffirm the clinical potential and to advance quantitative algorithms for BC diagnosis. Yet, the lack of a commercially available forward-looking OCT probe may be a threat to further development.

Upper Urinary Tract Cancer

Upper urinary tract cancers are almost exclusively upper tract urothelial carcinomas (UTUC). It is a rare disease with an incidence of about 2 cases per 100,000 people [30]. The histopathology of benign and malignant tissue in the upper urinary is highly similar to bladder urothelium. The normal intraluminal lining of the upper urinary tract consists of a few well-organized urothelial cell layers. The LP is clearly demarcated on each site by either the urothelium or the smooth muscle layer. Malignant urothelium is characterized by a tendency towards disorganization of urothelial cells and undefined tissue borders in case of invasiveness [14].

Ureteroscopic tissue biopsies are essential for the diagnostic process. Tumor grade and stage are decisive factors in the choice between radical nephroureterectomy (RNU) and kidney-sparing treatment [30]. However, ureteroscopic biopsy in the upper urinary tract is challenging due to the restricted range of motion of the instruments, the risk of complications, and the restricted sampling. Together with interpretation problems due to the limited biopsy volume, fragmentation and inter-observer variability, up to 20% of upper urinary tract biopsies are inconclusive. This results in limited reliability of UTUC grading and staging by ureteroscopic biopsies [31, 32].

Literature regarding the use of OCT in the upper tract is scarce. The systematic search yielded 6 relevant articles, of which 2 were overlapping studies [9, 25, 33–35]. Moreover, two studies primarily investigated the use of OCT for renal cancer diagnostics [34, 35]. An additional article that

Fig. 2 OCT scans of bladder cancer [published by Karl et al. in *Eur. J. Med. Res.* 2010]. Legend: **a** OCT brightness scan of normal bladder tissue with delineation of tissue layers, **b** OCT brightness scan of muscle-invasive urothelial carcinoma. Note that tissue layer identification is not possible due to the invasive character of the urothelial carcinoma

Table 3 Overview of studies on OCT for human upper tract urothelial carcinoma

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE IDEAL stage
Bus et al., 2016	Prospective cohort, in vivo	Assessment of ureteroscopic OCT for UTUC diagnosis	26 (26)	Illumien OCT, 2.7 Fr Dragonfly sideward-looking probe, 15 μ m AR, 1300 nm λ	RNU	OCT enabled visual staging of UTUC with 83% concordance with the final histopathology. Sensitivity and specificity for tumor invasion were 100% and 92%. Exophytic tumor growth greater than 2 mm and inflammation caused false-positives. In vivo OCT is feasible and enables wall delineation of normal and malignant upper urinary tracts.	A μ OCT cutoff of 2.4 mm ⁻¹ yielded a sensitivity of 87% and a specificity of 90% for differentiation of low- and high-grade UTUC. μ OCT analysis was not feasible for normal urothelium and CIS.	2b 2b
Mueller-Lisse et al., 2016	Prospective cohort, in vivo	Delineation of the UT wall layers	12 normal UT, 3 UT-UC (na)	M2 OCT system, 400 μ m sideward-looking probe, 15 μ m AR, 1300 nm λ	Ureteroscopic biopsies	NP		2b 2a
Ikeda et al., 2013	Case report, ex vivo	Feasibility study for UTUC diagnosis	1 (1)	3D UHS forward-looking OCT, 23 μ m AR, λ na	RNU	Visual differentiation of the tissue layers in the normal ureter. Lack of structural layers in muscle-invasive UTUC.		5 1
Tearney et al., 1997	Case series, ex vivo	Feasibility study of OCT in normal post-mortem ureters	5 (na)	OCT, 16 μ m AR, 1300 nm λ	Post-mortem resection	Visual differentiation of the mucosa, muscular layers, and adventitia of the normal ureter. The muscular layers had a higher and more regular backscattering intensity than mucosal and adventitial layers.		5 1

μ OCT: attenuation coefficient; λ , wavelength; AR, axial resolution; LoE, level of evidence; na, not available; NP, not performed; OCT, optical coherence tomography; RNU, radical nephroureterectomy; ROI, region of interest; UTUC, upper tract urothelial carcinoma; UT, upper tract

Fig. 3 OCT brightness scans & histopathology of UTUC and penile cancer. Legend: A1 + 2) Intraluminal OCT brightness scan & histopathology of a stage pTa UTUC with a continuous lamina propria (indicated by arrows in OCT brightness scan). B1 + 2) Intraluminal OCT brightness scan & histopathology of a pT2 UTUC with a disrupted lamina propria & heterogeneous backscattering (indicated by an arrow in OCT brightness scan). C1 + 2) OCT brightness scan & histopathology of a penile intraepithelial neoplasia with broadened epithelium (indicated by a double arrow in OCT brightness scan) adjacent to normal epithelium (single arrow)

investigated OCT in normal UT and UTUC was identified by snowballing [36]. The studies that primarily investigated OCT for UTUC are presented in Table 3.

Already in 1997, ex vivo OCT imaging of the upper urinary tract was investigated [25]. Visual tissue layer identification, as observed in the bladder, was confirmed for normal UT and invasive UTUC [33–36].

The development the sideward-looking OCT probes for intravascular imaging has enabled the use of OCT during ureterorenoscopy [9, 36]. In this way, real-time endoluminal OCT imaging enables visualization of UTUC and the layered tissue anatomy (Fig. 3). Interruption and loss of anatomical layers are characteristic for invasive UTUC. Bus et al. reported a concordance of 83% for qualitative tumor staging on OCT images in comparison to the RNU histopathology [9]. In the same study, quantitative μ_{OCT} analysis leads to differentiation between low- grade and high-grade UTUC. A μ_{OCT} cutoff value of 2.4 mm^{-1} for the differentiation of low- and

high-grade UTUC resulted in a sensitivity of 87% and a specificity of 90%. However, μ_{OCT} analysis was not feasible for normal urothelium and CIS. The infeasibility to measure the change of OCT signal with imaging depth might be caused by the thinness of the urothelial layer in these cases. Moreover, tumor staging was restricted to exophytic tumors of < 2 mm depth due to the limited OCT imaging range [9]. Another drawback was that the sideward-looking probe requires a parallel position with the tissue of interest for OCT imaging. This may impair the visualization of the calyceal cavities with OCT. Nevertheless, this LoE 2b study at IDEAL stage 2b showed that OCT has a high diagnostic accuracy and clinical potential for perioperative UTUC grading and staging [9]. Future research should be warranted. The development of a combined sideward- and forward-looking probe may overcome current technical limitations in the application of the technique for UTUC diagnosis.

Table 4 Overview of studies on OCT for human kidney cancer

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE IDEAL stage
Ludwig et al., 2017	Prospective cohort, ex vivo	Evaluation of OCT for PN margin assessment during	15 (na)	Diagnostic Photonics OCT, handheld probe, < 20 μm AR, λ na	PN	Measuring the margin widths with OCT was in concordance with the histopathological margin width assessment	The median μ_{OCT} of tumor was significantly higher than adjacent normal renal parenchyma (5.43 vs 3.78 mm^{-1}). All 15 PN cases had negative margins on both OCT analysis and final pathology	2b 2a
Buijs et al., 2017	Prospective cohort, in vivo	Assessment of μ_{OCT} of needle-based OCT for diagnosis of RMs	95 (95)	Ilumien OCT, 2.7 Fr RN, PN, or second probe, 15 μm AR, 1300 nm λ biopsy	RN	NP	The median μ_{OCT} of oncocytoma was 3.38 mm^{-1} . The median μ_{OCT} of RCC was significantly higher (4.37 mm^{-1}). Sensitivity and specificity for μ_{OCT} differentiation between benign and malignant RMs were 92% and 67%. The diagnostic yield of needle-based OCT was 99%.	2b 2b
Jain et al., 2015	Prospective cohort, ex vivo	Assessment of visual analysis for diagnosis of RMs	20 (20)	FF OCT light-CT scanner, 0.8 μm AR, λ na	RN	RCC showed heterogeneous appearances on OCT images but reliable qualitative differentiation was challenging. Invasive UTUC and AML were distinguishable on OCT images.	NP	2b 2a
Barwari et al., 2012	Prospective cohort, in vivo & ex vivo	Assessment of μ_{OCT} for diagnosis of RMs	16 (16)	Santec Innervision 2000; 7 Fr sideward-looking probe, 9 μm AR, λ na	RN	NP	The median μ_{OCT} of normal renal parenchyma was 2b significantly lower than that of malignant tumors (5.0 vs 8.2 mm^{-1}).	2b 2a
Lee et al., 2012	Prospective cohort, ex vivo	Feasibility study of OCT for the assessment of kidney morphology	19 (35)	Prototype integrated OCT; 4 μm AR, λ na	RN	By visual assessment, three pathologists achieved a sensitivity and specificity from 88 to 100% for differentiation of benign and malignant RMs with a substantial inter-observer agreement.	NP	2b 2a
Linchan et al., 2011	Prospective cohort, ex vivo	Feasibility study of OCT to characterize RMs	20 (38)	Laboratory OCT system; 4 μm AR, 890 nm λ	RN	RCC and subtypes of RCC lacked anatomical elements in comparison to normal parenchyma. Invasive UTUC, oncocytoma, and AML show distinctive appearances on OCT images.	NP	2b 2a
Barwari et al., 2011	Prospective cohort, ex vivo	Feasibility of μ_{OCT} for diagnosis of RMs	18 (26)	Santec Innervision 2000 OCT; 7 Fr sideward-looking probe, 9 μm AR, λ na	RN	NP	Mean μ_{OCT} of normal renal tissue (4.95 mm^{-1}) significantly lower than μ_{OCT} of RCC (4.95 vs 8.86 mm^{-1}).	2b 2a

μ_{OCT} : attenuation coefficient; λ : wavelength; AR, axial resolution; LoE, level of evidence; na, not available; NP, not performed; OCT, optical coherence tomography; PN, partial nephrectomy; RCC, renal cell carcinoma; RM, renal mass; RN, radical nephrectomy; ROI, region of interest; UTUC, upper tract urothelial carcinoma

Fig. 4 Needle-based OCT brightness scans & histopathology of renal tissue and prostate tissue. Legend: A1 + 2) In vivo OCT brightness scan & histopathology of renal angiomyolipomas. B1 + 2) In vivo OCT brightness scan & histopathology of renal oncocytoma. C1 + 2) In vivo OCT brightness scan & histopathology of clear cell RCC. D1 + 2) Ex

vivo OCT brightness scan & histopathology of prostate stroma. E1 + 2) Ex vivo OCT brightness scan & histopathology of benign glandular prostate. F1 + 2) Ex vivo OCT brightness scan & histopathology of prostate cancer Gleason 4 + 4

Kidney Cancer

Throughout the past decades, we have witnessed an increase in kidney cancer, mostly at the expenses of small renal masses (SRM, < 4 cm) [37]. About 90% of all kidney cancers are renal cell carcinomas (RCC), arising from the renal parenchyma. Multiple subtypes with heterogeneous clinical behavior can be identified by histo-morphologic features, micro-anatomic origin, and molecular alterations [38]. Clear cell RCC (ccRCC) is the most common subtype accounting for 75–80% of all RCCs. Its characteristic clear cell appearance is caused by the lipid and glycogen-rich cytoplasm [14]. Papillary RCC (pRCC) with a tubulopapillary architecture and chromophobe RCC (chRCC) are found in 10% and 5% of RCC patients, respectively [39]. Other more rare RCC subtypes, invasive UTUC, and benign tumors may also be the underlying pathology of renal masses.

Analysis of resected renal masses revealed 17–40% of benign pathology, mostly angiomyolipomas and oncocytomas [40]. This implies a clinically significant issue of preoperative misclassification [40]. As benign RM and cT1 RCC qualify for nephron-sparing treatment, preoperative renal mass biopsies (RMB) are gaining interest in the diagnostic algorithm. However, while accurate in terms of histologic reliability, RMB have a non-diagnostic rate of up to 23%, which is negatively correlated with RM size [41, 42]. This shortcoming highlights the need for a test with a high diagnostic yield and accuracy to avoid unnecessary treatment or repeated biopsies.

Based on the systematic search, 9 relevant articles were identified, of which 2 had overlapping populations (Table 4) [34, 35, 43–47].

In the first studies, qualitative assessment of ex vivo OCT images for the diagnosis of RCC was challenging because of

the heterogeneous appearance of RCC and the lack of distinctive OCT features [34, 35, 44]. Qualitative differentiation was only feasible in AML, oncocytomas, and invasive UTUC, where microarchitectural changes were recognizable [34, 35]. AML showed characteristic features of fat, which appeared as hypodense areas (Fig. 4). Oncocytomas demonstrated cystic areas and lobulated structures (Fig. 4) [34, 35]. In another study, qualitative OCT image assessment by three independent observers yielded a range in sensitivity and specificity from 88 to 100% for the differentiation of oncocytomas from RCCs [44].

Also, quantitative μ_{OCT} analysis of OCT images, which were acquired during laparoscopy or percutaneous needle-based imaging, has been investigated for RCC diagnosis. Studies have shown that the μ_{OCT} of RCC was significantly higher than normal renal parenchyma [43, 45, 46]. Buijs et al. investigated the diagnostic accuracy and yield of RMBs and concomitant in vivo percutaneous needle-based OCT imaging with sideward-looking probes in comparison to the histopathology of the resected specimen [46]. In their interim analysis cohort of 95 patients, μ_{OCT} analysis from percutaneous needle-based OCT led to a diagnostic yield of 99%, compared to a 79% diagnostic yield for conventional RMBs. For differentiation between benign and malignant RMBs, μ_{OCT} showed a sensitivity of 91% and a specificity of 56%. For the differentiation of RCC from oncocytoma, a sensitivity of 92% and a specificity of 67% were reported [46]. Since RMB is accompanied with a high non-diagnostic rate in smaller tumors, authors suggest that percutaneous needle-based OCT can potentially function as an add-on test or even as a replacement test in this niche of non-diagnostic cases.

Quantitative μ_{OCT} analysis has also been evaluated for ex vivo assessment of surgical margins during partial nephrectomies. Authors demonstrated a high accuracy for identifying

Table 5 Overview of studies on OCT for human prostate cancer

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE IDEAL stage
Muller et al., 2016	Prospective cohort, ex vivo	Feasibility study of needle-based OCT for prostate cancer	6 (na)	Illumien OCT, 2.7 Fr sideward-looking probe, 10 μ m AR, 1300 nm λ	RP with a slicing tool for one-to-one matching with OCT images	NP	Prostate cancer detection based on the μ oct was feasible. The μ oct for benign prostate tissue was significantly lower than in malignant prostate tissue (3.56 vs 3.85 mm ⁻¹).	2b 2a
Lopater et al., 2015	Prospective cohort, ex vivo	Assessment of OCT-based cancer detection in prostate biopsies	38 (119)	Full-field OCT system, forward-looking probe, AR na, λ na	Systematic core biopsy	A sensitivity of 63% and a specificity of 74% for NP visual cancer detection in core biopsies with OCT. Micro-focal prostate cancer may be missed with OCT.		2b 2b
Dangle et al., 2009	Prospective cohort, ex vivo	Feasibility study to assess surgical margins & extra capsular extension in RP	100 (na)	Niris OCT, 8 Fr forward-looking probe, 10–20 μ m AR, 1310 nm λ	RP	Identifying positive margins after radical prostatectomy with OCT yielded a sensitivity of 70% and a specificity of 84%. Heterogeneous, low scattering columns on OCT images characterized areas of tumor invasion.	NP	2b 2a
D'Amico et al., 2000	Prospective cohort, ex vivo	Characterizing prostate carcinoma in OCT images	7 (na)	Forward-looking OCT, 1 μ m AR, 800 nm λ	RP	OCT can visualize the microarchitecture in benign and malignant prostate tissue up to an imaging depth of 0.5 mm. Prostate cancer was characterized by smaller glandular lumens than in benign tissue.	NP	3b 1

μ_{OCT} : attenuation coefficient; λ , wavelength; AR, axial resolution; LoE, level of evidence; na, not available; NP, not performed; OCT, optical coherence tomography; ROI, region of interest; RP, radical prostatectomy

Table 6 Human studies on OCT for penile carcinoma

Author, year	Study type	Study aim	Sample size (ROI)	OCT system	Reference standard	Findings of qualitative OCT assessment	Findings of quantitative OCT analysis	LoE	IDEAL stage
Wessels et al., 2015	Prospective cohort, in vivo	Feasibility study for diagnosis of (pre)malignant penile lesions	18 (18)	Santec Inner Vision 2000 forward-looking OCT, 10 μm AR, 1300 nm λ	Punch biopsy	Visual assessment of tissue layers served to discriminate between benign and malignant lesions. Mean epidermal thickness measured on OCT images of benign lesions was 0.18 mm versus 0.53 mm in (pre)malignant lesions ($p = 0.001$).	Mean μOCT of benign lesions was significantly lower than in (pre)malignant lesions (2.5 vs 5.2 mm^{-1}).	2b	2a
Schmitz et al., 2014	Case report, in vivo	Feasibility study of OCT in premalignant penile lesions	1	Vivosight multibeam forward-looking OCT, 10 μm AR, λ na	Punch biopsy	The dermo-epidermal junction zone can be visualized to determine invasiveness. Local treatment response can be evaluated visually with OCT.		NP	1

μOCT : attenuation coefficient; λ , wavelength; AR, axial resolution; LoE, level of evidence; na, not available; NP, not performed; OCT, optical coherence tomography; ROI, region of interest

positive margins (sensitivity and specificity both 100%), although the value was limited by a small sample size [47].

As such, quantitative μOCT analysis for renal mass diagnosis has diagnostic potential. OCT adjunct to RMBs may enhance the diagnostic yield to improve the diagnostic pathway, with a possible “best benefit trade-off” in SRMs. The literature on OCT is still limited to LoE 2b at IDEAL stage 2b but respectable clinical cohort samples have been investigated.

Prostate Cancer

Prostate cancer (PC) is the most common cancer in men [48]. In 95% of the cases, PC is an adenocarcinoma. Other types of PC are small cell carcinomas, urothelial carcinomas, squamous, or basal cell carcinomas [14]. In the normal prostate gland, non-glandular and glandular tissues are interbred. Normal glandular tissue consists of organized stroma with smooth muscle fibers and well-organized glandular acini and ducts. Normal acini and ducts share a well-established microarchitecture of secretory, basal, and neuro-endocrine cells. Adenocarcinomas originate in 80% of the cases from acini or ducts [14]. Malignancy is characterized by a tendency towards disorganization, loss of architecture, and lack of basal cells. The Gleason-score and the corresponding grade groups are used to evaluate the grade of malignancy based on the architectural and morphologic alterations [49]. Prostate biopsies are the reference standard for PC diagnosis. However, the accuracy of tumor localization and demarcation of the current diagnostic approach is limited due to the multifocal nature of PC. Especially in the scope of focal therapies, exact identification of prostate cancer foci is required, driving the interest in new imaging modalities.

Six relevant articles on OCT in PC were identified with the systematic search, of which 3 use the same overlapping population (Table 5) [8, 50–52]. The first OCT on human prostates was performed in an ex vivo study in 2000 [50]. OCT allowed demarcation of the prostatic microarchitecture [50, 52]. Visualization of irregular gland contours, the infiltration of benign glands, or the visualization of cribriform patterns was the characteristic for PC on OCT images, demonstrating a sensitivity and specificity of 63% and 74%, respectively [47]. However, micro-focal PC may be missed with OCT, although the clinical implication of these foci is unknown [52].

In 2016, the feasibility of quantitative μOCT -based PC diagnosis for potential percutaneous needle-based OCT of PC was investigated in prostatectomy specimen with sideward-looking OCT probes in a needle-based fashion [8]. In this study, a customized tool for histopathology slicing was used for exact co-localization of the histopathology with OCT images (Fig. 4). Despite the limited sample size, the μOCT in PC was significantly higher than in benign prostate tissue [8].

OCT was also investigated for the assessment of surgical margins after robotic prostatectomy in 100 patients with a

forward-looking OCT device [51]. In this study, OCT-based predictions for the assessment of surgical margins were compared to the histopathology of the radical prostatectomy, yielding a sensitivity of 70% and a specificity of 84% [51]. OCT characteristics for positive margins were seen as heterogeneous columns of low signal intensity extending from the subepithelium to the surface of the serosa.

On balance, OCT has reached LoE 2b at an IDEAL stage 2a in ex vivo studies, where visual assessment of OCT images and quantitative μ_{OCT} analysis allow for PC identification [12]. Yet, translation to in vivo studies for PC diagnosis is lacking, possibly because the additional value of OCT for PC diagnosis may be marginal when considering the improvements of radiology-guided biopsies. A possible role for OCT in PC might be intraoperative assessment of surgical margins during radical surgery.

Testicular Cancer

Testicular cancer is the most prevalent solid cancer in young men. In 95% of the cases, testicular cancers are germ cell tumors, mostly seminomas and non-seminomas [14]. Ultrasound of the scrotum is the index test for initial diagnosis. In case of suspicious tumors, inguinal orchiectomy is diagnostic and therapeutic. Testicular biopsies are not considered in the presence of a normal contralateral case due to the risk of tumor seeding. According to our systematic search, OCT has not been investigated in testicular cancer. A hypothetical use of OCT in testicular tumors is the perioperative assessment of resection margins in partial orchiectomy.

Penile Cancer

Penile cancer (PeC) is a rare disease in the Western World. It usually arises from malignancy of the epithelium of the glans or the prepuce. PeC is almost exclusively squamous cell carcinomas (SCC), although it may exhibit different morphologies. PeC presents as superficial horizontal growth, superficial exophytic growth, or invasive growth into deeper tissue layers [14]. SCC may be preceded by penile intraepithelial neoplasia (PIN). This pre-malignancy is characterized by a disorganized basal layer of the epithelium [14]. Punch biopsies are the reference standard for diagnosis.

Only 2 relevant articles were identified from the systematic search. A case report described the first use of OCT in premalignant penile lesions. The continuous dermo-epidermal junction zone of the superficial premalignant lesion was visualized and the local chemotherapy response was monitored [53]. A prospective cohort study with LoE 2b at IDEAL stage 2a evaluated the use of OCT for the diagnosis of suspicious penile lesions (Table 6). OCT images of suspicious penile lesions were compared to histopathology of punch biopsies in 18 patients. Besides qualitative assessment of the integrity of

tissue layers, quantification of the epidermal thickness and μ_{OCT} analysis enabled PeC diagnosis (Fig. 3) [54]. Despite the limited evidence of this single study of 2b LoE, OCT seems to have a promising diagnostic potential with a high clinical practical value for PeC and PIN.

Discussion

With regard to the diagnostic potential of OCT in urologic oncology, the present appraisal on the current state of development of OCT shows an overall LoE 2b and up to 2a–2b IDEAL stages for all major urologic cancers with the exception of testis cancer. Overall, the current evidence indicates that OCT holds the potential as a replacement or add-on test for the diagnostic pathways in BC, UTUC, RCC, and PeC. However, the setting is still exploratory as studies are predominantly single-center studies with restricted and heterogeneous samples, OCT methodology and technologic application. In some uro-oncological diseases, the technical level has not yet met all clinical requirements, and optimized OCT systems for urologic applications are still lacking. Nevertheless, in the light of some promising results and potential clinical practicality, further research should be fueled on OCT in most urologic oncology conditions. Future research and clinical implementation of OCT will eventually depend on thorough appraisal of the potential diagnostic gains, clinical availability, and costs in comparison with the index tests. Notably, we should catch the wave to combine different optical imaging techniques for a multimodal optical biopsy approach. Multimodal optical assessment, especially in combination with computer-aided diagnosis, could boost the additional diagnostic value of the new techniques with regard to the conventional diagnostic paradigms.

In BC, transurethral resection is concomitantly diagnostic and therapeutic. As such, OCT may only be of an additional value during cystoscopy to provide histologic certitude for discharge, continuing routine follow-up, expectative policy, or outpatient laser vaporization of low-risk BC. However, the current state of development of OCT is hampered by the lack of a commercially available forward-looking probe.

In UTUC, the potential of OCT as an add-on or even replacement test for ureteroscopic biopsies seems alluring. OCT holds a high clinical and practical value for UTUC diagnosis because of its real-time character and the limited diagnostic yield and clinical burden of ureteroscopic biopsies. Especially, quantitative tumor grade differentiation could provide practical and objective intraoperative risk-stratification for adequate selection and immediate ureteroscopic treatment. Therefore, validation studies and phase III trials as well as technical development of a combined sideward- and forward-looking probe should be encouraged. Yet, the cost-effectiveness may be at risk as UTUC is a rare disease.

Within the scope of the ongoing discussion on the role of RMB, especially in SRMs, OCT could be applied as an add-on test to improve the diagnostic pathway. Further research to validate quantitative outcomes for μ OCT-based diagnosis should be undertaken. Again, one should carefully balance the value of this add-on benefit versus the additional costs. Moreover, OCT could be used for intraoperative assessment of surgical margins in partial nephrectomies.

In PeC, OCT could serve as a non-invasive replacement test for punch biopsies of suspicious penile lesions. Furthermore, OCT might even enable monitoring of the topical treatment response in PIN. Despite the low incidence of PeC, further research should be stimulated to evaluate its diagnostic value. In view of the frequent centralized care of PeC and the use of re-usable handheld OCT devices, the cost-effectiveness of OCT for PeC could be reasonable.

The role of OCT for PC diagnosis or image guidance adjunct for prostate biopsies seems limited in an additional diagnostic value. The combination of radiologic imaging with systematic and targeted biopsies represents a fierce competitor for optical imaging in PC diagnosis [55]. Yet, OCT could provide real-time histologic information. However, translation to in vivo diagnostic studies is lacking. Only one in vivo study for OCT-based assessment of resection margins in prostatectomies has been performed. Future research should define the role of OCT in PC.

At present, no OCT information is available for the diagnosis of testicular cancer. Because percutaneous diagnostic biopsy is not indicated, it is likely that the role of OCT will be limited at the most to perioperative assessment of the surgical margins during partial orchiectomy.

Overall, the strength of this comprehensive review is the systematic elaboration of the current state of development of OCT in all major uro-oncological diseases. However, the lack of high-level evidence, as well as the heterogeneity of study populations and technical data, limits the feasibility of a sound systematic review. Hence, conclusions are based on the first stages of the evaluation of a new technology. However, a thorough evaluation should be mandatory before clinical implementation. Moreover, early identification of conditions in which OCT may be most beneficial may stimulate and catalyze future developments. As such, this review will guide further translational research towards the implementation of OCT into uro-oncological practice.

Author Contribution J.E. Freund: Project development, data collection and management, manuscript writing

M. Buijs: Data collection, manuscript writing

C.D. Savci-Heijink: Project development, manuscript editing

D.M. de Bruin: Data collection, manuscript editing

J.J. de la Rosette: Project development, manuscript editing

T.G. van Leeuwen: Project development, manuscript editing

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Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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

Appendix 1

An individual search was performed for each organ in Pubmed and Embase for English and German articles up to December 2017. For each search, the key terms for OCT {OR} were combined {AND} with organ-specific key terms {OR}.

Optical coherence tomography (Mesh)

Optical coherence tomography

OCT

Urinary Bladder Neoplasms (Mesh)

Bladder neoplasm

Bladder tumor

Bladder cancer

Bladder carcinoma

Bladder malignancy

Urothelial carcinoma AND {Ureter OR Renal pelvis}

Transitional cell carcinoma AND {Ureter OR Renal pelvis}

Upper urinary tract tumor

UTUC

Urinary tract tumor

Urinary tract cancer

pelvis tumor

Ureter tumor

Renal Cell Carcinoma (Mesh)

Renal neoplasm

Renal tumor

Renal mass

Renal cancer

Renal carcinoma

Renal malignancy

Kidney neoplasm

Kidney tumor

Kidney mass

Kidney cancer

Kidney carcinoma

Kidney malignancy

Prostatic Neoplasms (Mesh)

Prostate tumor

Prostate cancer

Prostate malignancy

Testicular Neoplasms (Mesh)

Testicular tumor

Testicular cancer

Testicular carcinoma

Testicular malignancy
Testis neoplasm
Testis tumor
Testis cancer
Testis carcinoma
Testis malignancy
Penile Neoplasms (Mesh)
Penile tumor
Penile cancer
Penile carcinoma
Penile malignancy
Penis neoplasm
Penis tumor
Penis cancer
Penis carcinoma
Penis malignancy

Flow diagram for study selection:

Legend: *BC*, bladder cancer; *UTUC*, upper tract urothelial carcinoma; *RCC*, renal cell carcinoma; *PC*, prostate cancer; *TC*, testicular cancer; *PeC*, penile cancer

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