REVIEW PAPER

UROLOGICAL ONCOLOGY

Optical coherence tomography diagnostics for onco–urology. Review of clinical perspectives

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Introduction. Optical coherence tomography (OCT) is being investigated widely for use in urologic pathology. The current imaging of urogenital cancers cannot be perfect, thus, routine methods demands new updates or inventions of alternative radiological scope. OCT presents so–called "live" optical biopsy. The authors aim to review this modality for uro–oncological purposes.
Matherial and methods. A series of 37 publications between 1989 and 2012 was selected and cited from GoogleScholar and PubMED/MEDLINE. The urogenital tract (bladder, ureter, scrotum organs and prostate) was imaged by OCT.
Results. The overall OCT sensitivity, specificity, accuracy, negative and positive predictive values ranged a lot on example of the urinary bladder's tumors screening. The data were 75–100%, 65–97.9%, 92%, 75%, 100%, respectively. Notwithstanding, a diagnostic importance of OCT may be comparable with urine cytology, cystoscopy, computerized tomography and magnetic resonance imaging.
Conclusions. OCT demonstrated its imaging potential, while till the present OCT plays role of an additional imaging. Future progress of OCT involvement in experimental and clinical once–urological diagnostics is needed under high evidence control.

Key Words: optical coherence tomography ‹› urology ‹› oncology

INTRODUCTION

Optical Coherence Tomography (OCT) was first applied as a method for generating 3–D tomograms of the eye structures in 1991 by Fujimoto and collogues [1]. Since this date OCT, has been steadily gaining popularity opening new frontiers in medical imaging due to its phenomenal spatial resolution enabling tissue pathology to be precisely imaged *in situ* and in real time. OCT acquired images may reach 200 x 200 pixels, 11µm depth resolution in tissue, and 25µm lateral resolution. This means that OCT provides an order of magnitude higher spatial resolution than ultrasound or Micro–MRI, while imaging an order of magnitude deeper than that of confocal/multiphoton microscopy [2]. The ability of acquiring such high resolution cross sectional imaging has already found a lot of application in modern ophthalmology. In case of urology, OCT is an still experimental method of diagnosing diseases of urogenital tracts, however, its potential is being gradually uncovered.

OCT in urology imaging

The clinical potential of OCT has not yet been completely revealed for patients with onco–urological lesions. OCT became a new trend for non–ophthalmological use, which is entering widely to resolve imaging clinical tasks, particularly in the imaging of all the urinary tract's layers [3, 4]. So far this

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technique has been cleared by the Food and Drug Administration for imaging of the anterior segment of the eye and further studies are needed to extend its reliable use [5]. Over the past decade, about 500 million US dollars were spent on federally funded research in order to improve OCT technology and increase its popularity in modern medicine [6]. A great scientific interest arises from the use of OCT in diagnostics and in both real–time and postoperative assessments at a tissue level, because this modality has its own physical features that have made it a unique visualization instrument. Nevertheless, OCT also has several minor limitations that include a high cost and low penetration depth and angle.
The noninvasive nature of image acquisition, together with the commercialization of systems optimized for clinical use has resulted in a steady increase in the use of OCT imaging in urology. Its image resolutions of one to two orders of magnitude higher than conventional ultrasound and the ability to conduct the *scan in situ* and in real time are features that are particularly useful in imaging of the urogenital tracts [7]. Miniaturization of OCT has led to its application in endoscopic use has enabled high–resolution intraluminal imaging of urinary tracts [8]. Catheter–based, intraluminal probes for OCT have provided a new possibility of distinguishing between the urothelium, lamina propria, and muscle layer allowing the detection of lesions and staging in real time without the need for biopsy. OCT may serve as an instrument dedicated to "optical biopsy" to image tissue microstructure with a resolution comparable to that of a standard excisional biopsy and histopathology [9].

Optical biopsy

The effectiveness of cancer therapy depends strongly on the early identification of neoplastic changes. Histopathology and excisional biopsy both remain gold standards for cancer diagnostics and have both had a substantial impact on the diagnosis and treatment of neoplastic changes. Unfortunately, diagnostics based on biopsies is prone to sampling errors, which in turn cause high false negative rates. A potential solution of this disadvantage is to image at a resolution comparable to histopathology, but without the need for tissue removal – in other words, to introduce a technology, which would be capable of performing a so–called "optical biopsy"[10]. Such new instrumentation could improve the detection of neoplastic changes at treatable stages by providing information, obtained at different orientations, in a manner analogous to ultrasound. A modern imaging modality that may be feasible to perform such diagnostics is optical coherence tomography (OCT). This technique is able to provide high–resolution optical imaging of unstained human tissue morphology. It has been already demonstrated that OCT demonstrates an opportunity to image human normal tissues of the urinary tract and the genital system, such as: kidney, ureter, bladder, prostate, and male genitalia [11–19].

OCT – basic concept

The major concept of OCT technology is analogous to ultrasound. The OCT performs high–resolution, cross–sectional tomographic imaging of the internal microstructure of diagnosed organs by measuring backscattered or backreflected light. Laterally the mechanism of data acquisition is analogous to ultrasound B mode imaging except that it uses infrared light instead of sound, when a beam of sound is directed onto tissue, it is backreflected or backscattered from structures that have different acoustic or optical properties as well as from boundaries between structures [20]. The collected signal is then combined with a reference signal and both are used to generate a high spatial resolution image of the tissue microstructure. Due to the extremely high speed of light, direct measurement of the time delay between short light pulses cannot be performed electronically – in contrast to ultrasound. Therefore, to reconstruct the morphology of the measured object, interferometric correlation techniques are required. The resolution of OCT technology depends on the optical design of the system and light source and may vary from 20 microns (μm) up to 1 μm. The image penetration depth of OCT is up to 2–3 mm in tissue [21]. Finally, OCT data are generated in digital form, facilitating the use of electronic storage and transmission of data as well as advanced image processing.

MATERIAL AND METHODS

Previous endoscopic studies demonstrated that OCT imaging could be integrated with endoscopic procedures also when applied to uro–oncology. However, it is still questionable whether this technique is able to provide valuable diagnostic information. In this article we aimed to summarize and criticize the existing literature data in terms of diagnostic potentials or possible perspectives of OCT in uro–oncology.
All selected materials were achieved on–line, search has been performed using medical search engines GoogleScholar and PubMED/MEDLINE. All the literature was dated between 1989 and 2012. Finally, the authors analyzed 37 clinical papers.

Table 1. *Radiological profile for OCT of the urinary bladder malignancy*

Characteristics	Sensitivity (Range, %)	Specificity (Range, %)	Positive predictive value, %	Negative predictive value, %	Accuracy, %
Overall for bladder tumors [20,18]	75–100	65–97.9	75	100	92
Specific for superficial tumors [19]	75–90	89–97	–	–	–
Specific for muscle–invasive tumors [17,19]	100	90	–	100	–

RESULTS

The studied literature was observational in nature, no multicentral evidence references were provided. The Author's summed up the results separately.

Bladder

To date, the authors would consider the urinary bladder as a main organ for OCT applications. The technical precisions have been analyzed (Table 1). It was necessary to emphasize the promising parameters of sensitivity and specificity of OCT to diagnose superficial tumors (Table 2). The OCT sensitivity ranges may be comparable with urine cytology and cystoscopy in the detection of non–muscle invasive cancer. The specificity of fluorescence cystoscopy was lower than OCT, whereas urine cytology had the highest one. The OCT specificity ranged. The maximum specificity of urine cytology exceeded that of OCT, being 99% and 97%, respectively. The cystoscopic specificity yielded to OCT. OCT scanning may be a relevant competitor with routine imaging (magnetic resonance imaging (MRI) and computerized tomography (CT)) for cancerous findings of the urinary bladder (Table 3). So, independently, the maximum OCT sensitivity was better than the CT and the same as with MRI. OCT seemed to persist with higher specificity than that of CT and MRI in maximum numbers. The MRI accuracy was the highest, however, the OCT accuracy took the lead over CT. Recently, the incorporation of OCT in diagnostic cystoscope was resolved technically in humans and models [34]. Experimental attempts for OCT post–operative checks of bladder cancer pathologies were performed (Table 4).

Ureter

The ureter has been explored chiefly on animal models [16, 35, 36]. Thus, Mueller–Lisse et al. described OCT differentiation between urothelium and deeper tissue layer of the porcine ureter [28]. In 2009, the same group compared OCT and endoluminal ultrasonography and found that ureteral OCT was significantly superior in the distinction of any wall layers ($P < 0.001$), urothelium and lamina propria ($P < 0.001$), and lamina propria and muscle layer ($P < 0.001$), but was inconclusive for the inner and outer muscle layer ($P < 0.001$; $P > 0.25$) [16]. This fact opened a road to OCT assistance for ureteroscopy in the human ureter wall [36].

Kidney

Onozato et al. presented OCT characterization of the tubules, glomeruli and cortical vessels with a penetration depth of up to 2 mm and 10 µm spatial resolution [13]. The study used human renal tissue and OCT documented histopathological changes in the tubules, glomeruli, and interstitium that closely matched the conventional histological observations. In addition, Linehan et al. detected some histological subtypes of benign (angiomyolipoma, oncocytoma) and malignant renal tumors (clear–cell, papillary and transitional cell carcinomas) on the glomerular and tubular level using OCT [11]. The first OCT–as-

Table 2. *OCT and classical methods of diagnostic evaluation of the bladder superficial tumors (carcinoma in situ included)*

Methods	Sensitivity (Range, %)	Specificity (Range, %)
OCT [17,18]	75–90	89–97
Urine cytology [18,19]	70–90	90–99
White light cystoscopy [22,23]	60.5–72.7	–
Fluorescence* cystoscopy 25–26	90.1–96.9	87.5

*– 5–aminolevulinic acid, hexaminolevulinate

Table 3. *Overall radiological characteristics of optical coherence tomography (OCT), magnetic resonance imaging (MRI) and computerized tomography (CT) of the urinary bladder tumors*

Method	Sensitivity (Range, %)	Specificity (Range, %)	Accuracy (Range, %)
OCT [17,18]	75–100	65–97.9	92
MRI [25,26]	82–100	62–76.5	73–93.65
CT [25]	94	62	80

Table 4. *The recent descriptive studies on bladder and prostatic OCT applications. PPV–positive predictive value, NPV–negative predictive value. Bladder Tumors (BT) staging: cTa–confined to mucosa, cT1– lamina propria infiltration, cT2 (MIBC) – muscle invasive bladder cancer, PCa – Prostate Cancer*

Source	Model (n)	Model f eatures	Organ and disease	Sensitivity (%)	Specificity (%)	Other Parameters
Karl et al. (2010) [18]	Human (52)	Diagnostic cystoscopy using OCT	BT	100	65	It detected no false negative lesions
Schmidbauer et al. (2009) [17]	Human (66)	Diagnostic cystoscopy using OCT, combination with hexaminolevulinate fluorescence cystoscopy	BT	97.5 (on a per–lesion basis); 100 (on a per–patient, overall)	97.9 (on a per–lesion basis)	–
Ren et al. (2009) [27]	Human (56)	Intra–operative cystoscopic OCT, comparison of OCT with cystoscopy and cytology	BT	94	81	–
Dangle et al. (2009) [28]	Human (100)	Post–operaitive prostatectomy specimens	PCa	70	84	PPV is 33% NPV is 96%
Segottayan et al. (2008) [29]	Human (32)	Diagnostic cystoscopy using OCT	BT	75 (for cT1); 100 (for cT2, MIBC)	97 (for cT1); 90 (for cT2, MIBC)	NPV for MIBC was 100%. Discrimination between malignant and benign lesions with PPV of 89% and NPV of 100%
Hermes et al. (2008) [30]	Human (142)	Post–operative specimens (RC, TUR–BT)	BT	83.8	78.1	The use of ultrahigh resolution OCT was used
Goh et al. (2008) [31]	Human (32)	Diagnostic cystoscopy	BT	90 (for pTa); 100 (for pT2)	89 (for pTa); 90 (for pT2)	MIBC (92% accuracy)
Yuan et al. [29] (2008)	Rat, Porcine, Human (–)	Diagnostic cystoscopy	BT	92	85	Time–domain OCT and spectral–domain OCT with advanced MEMS–mirror for endoscopic laser scanning imaging
Zagaynova et al. (2008)[19]	Human (164)	Diagnostic cystoscopy	BT	85	68	Time–domain OCT
Ketul et al. (2007) [33]	Human (50)	Post–operative imaging	PCa	75	78	PPV is 23%, NPV is 97%

sisted surgery was performed by Goel et al. who have put the renal OCT into surgical practice for laparoscopic partial nephrectomy [37].

Scrotal organs

OCT of the scrotum, in particular seminiferous tubules, the epididymis, and the vas deferens, has a high level of resolution, almost to the histopathological scale (15 *vs.* 3 μm) [38].

Ramasamy et al. proposed a rodent model with full field version of OCT to explore spermatogenesis within the seminiferous tubules in freshly excised testicular tissue, without the use of exogenous contrast or fixation [39].

These studies indicated OCT employment may facilitate visualization of spermatogenesis in humans and aid to minimize testicular trauma during micro–TESE. The limitations of OCT imaging were still the 2 mm depth of OCT signal penetration, a delayed image processing with artifacts, and the need to overcome the short learning curve for interpreting the OCT [38]. OCT has not been so far evaluated for imaging of testicular tumors.

Prostate

Several OCT investigational endeavors to develop an approach to the prostate were produced with the following results.

Initially, rat models were reported [40, 41]. Fried NM et al. explored the rat prostate and cavernous nerves [41]. Cross–sectional and longitudinal OCT images allowed differentiation of the cavernous nerves and ganglion with the surrounding prostate gland. OCT correlated with histology for real–time visualization of the cavernous nerves.

OCT of *ex vivo* human prostatectomy specimens illustrated architecture of the prostatic capsule and stroma, similar to the histological approach [42]. On human prostatic samples of resected cancer, OCT sensitivity was 70–75% and specificity was between 78 and 84%, the positive predictive value and negative predictive value were 23–33% and 96–97%, respectively [43].

In a clinical setting during open laparoscopic and robotic–assisted radical prostatectomies, Feldchtein F. et al. identified cancer and normal tissue retroperitoneal structures, including the ureter, with OCT [15].

CONCLUSIONS

In conclusion, OCT is becoming a unique modality for diagnostics of malignant lesions of the urogenital region, but the present data have not been tried in a manner adequate enough to understand all pros and cons. The OCT–assisted urological procedures are still under experimentation.

It is possible that OCT will compete with the standard diagnostic imaging (cystoscopy, CT, MRI) in sensitivity, specificity, and other characteristics. Today, different combinations of these radiological tools have not yet been studied. Forthcoming research has to clarify the radiological benefits of OCT to all specific uro–oncological areas in the frame of an evidence–based doctrine.

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