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Mieke T. J. Bus
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Sybren L. Meijer
Geert J. Streekstra
Dirk J. Faber
Guido M. Kamphuis
Patricia J. Zondervan
Marcel van Herk
Maria P. Laguna Pes
Maik J. Grundeken
Martin J. Brandt
Theo M. de Reijke
Jean J. M. C. H. de la Rosette
Ton G. van Leeuwen

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Ex-vivo study in nephroureterectomy specimens defining the role of 3-D upper urinary tract visualization using optical coherence tomography and endoluminal ultrasound

Mieke T. J. Bus,^{a,*} Paul Cernohorsky,^b Daniel M. de Bruin,^{a,c} Sybren L. Meijer,^d Geert J. Streekstra,^{c,e} Dirk J. Faber,^c Guido M. Kamphuis,^a Patricia J. Zondervan,^a Marcel van Herk,^c Maria P. Laguna Pes,^a Maik J. Grundeken,^f Martin J. Brandt,^c Theo M. de Reijke,^a Jean J. M. C. H. de la Rosette,^a and Ton G. van Leeuwen^c

^aUniversity of Amsterdam, Academic Medical Center, Department of Urology, Amsterdam, The Netherlands

^bUniversity of Amsterdam, Academic Medical Center, Department of Plastic, Reconstructive and Hand Surgery, Amsterdam, The Netherlands

^cUniversity of Amsterdam, Academic Medical Center, Department of Biomedical Engineering and Physics, Amsterdam, The Netherlands

^dUniversity of Amsterdam, Academic Medical Center, Department of Pathology, Amsterdam, The Netherlands

^eUniversity of Amsterdam, Academic Medical Center, Department of Radiology, Amsterdam, The Netherlands

^fUniversity of Amsterdam, Academic Medical Center, Department of Cardiology, Amsterdam, The Netherlands

Abstract. Minimal invasive endoscopic treatment for upper urinary tract urothelial carcinoma (UUT-UC) is advocated in patients with low-risk disease and limited tumor volume. Diagnostic ureterorenoscopy combined with biopsy is the diagnostic standard. This study aims to evaluate two alternative diagnostic techniques for UUT-UC: optical coherence tomography (OCT) and endoluminal ultrasound (ELUS). Following nephroureterectomy, OCT, ELUS, and computed tomography (CT) were performed of the complete nephroureterectomy specimen. Visualization software (AMIRA[®]) was used for reconstruction and coregistration of CT, OCT, and ELUS. Finally, CT was used to obtain exact probe localization. Coregistered OCT and ELUS datasets were compared with histology. Coregistration with three-dimensional CT makes exact data matching possible in this *ex-vivo* setting to compare histology with OCT and ELUS. In OCT images of normal-appearing renal pelvis and ureter, urothelium, lamina propria, and muscularis were visible. With ELUS, all anatomical layers of the ureter could be distinguished, besides the urothelial layer. ELUS identified suspect lesions, although exact staging and differentiation between noninvasive and invasive lesions were not possible. OCT provides high-resolution imaging of normal ureter and ureter lesions. ELUS, however, is of limited value as it cannot differentiate between noninvasive and invasive tumors. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.1.017001]

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1 Introduction

At present, nephroureterectomy is the reference standard for treatment of upper urinary tract urothelial carcinoma (UUT-UC). During the past decade, minimal invasive endoscopic treatments are recognized as a viable treatment option in selected cases with low-grade, noninvasive, UUT-UC, and limited tumor volume.¹ The advantage of endoscopic treatment is preservation of kidney function. The choice of treatment depends on accurate visualization and pretreatment information on grade and stage of suspected lesions. The contemporary mainstay in the diagnosis of UUT-UC is based on imaging [computed tomography urography (CT-U)], ureterorenoscopy (URS), biopsy, and urine cytology. CT-U has the highest diagnostic accuracy for the upper urinary tract with a sensitivity of 0.67 to 1.0 and specificity of 0.93 to 0.99. However, its accuracy decreases in cases of small lesions whereas flat lesions are not detectable unless they cause a filling defect or ureter thickening.² Unfortunately, histology obtained during URS is often inconclusive due to small biopsy samples and crush artifacts, and usually no frozen section on biopsy specimen is done

because of the limited and small biopsy specimens.³ If histological diagnosis, grading, and staging of UUT-UC are obtained intraoperatively, optimal patient selection and immediate decision on endoscopic conservative management might be possible. In addition, patients who receive a conservative treatment need to undergo a thorough follow-up consisting of URS, cytology, and imaging regularly according to the guidelines. A minimal invasive endoluminal imaging technique could possibly provide a more optimal, less invasive follow-up for patients and diminish the amounts of biopsies taken. A technology that provides simultaneous imaging of the ureter with high resolution and depth penetration could give this information. However, all imaging techniques suffer from a trade-off between imaging depth and resolution. Several technologies are studied for the upper urinary tract, including optical coherence tomography (OCT) and endoluminal ultrasound (ELUS). Each of these technologies harbors limitations. OCT produces high-resolution cross-section images of the ureter but has a maximal imaging depth of 1 to 2 mm. If tumor thickness transcends this limited imaging depth, tumor invasiveness cannot be assessed.⁴

*Address all correspondence to: Mieke T. J. Bus, E-mail: m.t.bus@amc.uva.nl

Table 1 Imaging properties of ELUS and OCT.

	ELUS	OCT
Contrast mechanism	Sound scattering	Light scattering
Aim	Real-time imaging of luminal structures	Real-time information on pathological diagnosis
Imaging depth (mm)	20 to 40	2 to 3
Resolution (μm)	Axial 200 Lateral 200 to 250	Axial 15 Lateral 20 to 40
Advantage	High-imaging penetration depth	Fast data acquisition High-resolution imaging Information on tumor grade and stage
Limitations	Slow data acquisition speed low-resolution imaging	Diminished imaging depth range

ELUS has an increased imaging depth compared to OCT (Table 1) but produces images of a low resolution.

Finally, the challenge in comparing serially acquired OCT with ELUS data is that no absolute colocalization can be attained without a second, common imaging modality for coregistration. Rapid coregistration can be achieved by automated pixel intensity-based image correlation software.⁵ However, due to serial introduction of the OCT and ELUS probe, the imaged ureter tissue can be shifted and altered and subsequently visualized differently. CT-based coregistration has the benefit of absolute spatial colocalization of two independently acquired datasets.⁶

We hypothesize that the high resolution of OCT increases the visibility of small structures and thin layers in the ureter itself, including urothelial layer, whereas the increased depth imaging of ELUS contributes to the visibility of tissue structures beyond 2 mm in depth. The first aim of this feasibility study is to investigate the use of CT for optimal coregistration of OCT and ELUS. The second aim of this study is to determine whether coregistered OCT and ELUS could improve visualization of large (>2 mm) upper urinary tract tumors and discriminates between noninvasive and invasive tumors, by performing coregistered OCT and ELUS measurements in five nephroureterectomy specimens of patients with proven UUT-UC. We compared individual OCT and ELUS datasets on their ability to visualize individual tissue layers of the ureter (urothelium, lamina propria, muscularis propria, and periureteral fat).

This study will be performed in the context of the first stage of the IDEAL model designed for evaluation of surgical techniques (1: innovation/idea, 2a: development, 2b: exploration, 3: assessment, and 4: long-term follow-up).^{7,8}

2 Material and Methods

Five complete resected nephroureterectomy specimens, including bladder cuff, of patients with biopsy confirmed UUT-UC

Fig. 1 Study setup: OCT measurement and ELUS measurements were performed during CT imaging. CT imaging allowed coregistration. This figure demonstrates our study setup while performing OCT measurements that were followed directly by ELUS measurements. \$: nephroureterectomy specimen, I: insertion of OCT probe in the ostium of the resected bladder cuff, O: OCT probe, A: during each measurement, saline was manually injected in by the probe into the ureter to ensure dilated lumen for optimal measurements, and H: OCT device. In total, five complete resected nephroureterectomy specimens, including bladder cuff, of patients with biopsy confirmed UUT-UC were examined using serial OCT and ELUS measurements combined with coregistered CT.

were examined using serial OCT and ELUS measurements combined with coregistered CT (Fig. 1).

Immediately after surgery, the specimens were transported to the radiology department to perform OCT, ELUS, and CT imaging. Following CT, OCT, and ELUS imaging, the specimens were transported to the pathology department for histopathological processing. This study was approved by the institutional review board in 2013, Academic Medical Center, Amsterdam. The institutional review board waived the need for written informed consent of the participants.

2.1 Optical Coherence Tomography Imaging

OCT images were obtained as described previously by our group.⁴ The OCT system used was the Illumien Intravascular Imaging System, interfaced to a C7 Dragonfly™ 2.7Fr (0.9 mm) Imaging Probe (St. Jude Medical, St. Paul, Minnesota) with an axial resolution of 15 μm and a lateral resolution of 20 to 40 μm .⁹ First, an OCT imaging probe was introduced through the ureteral orifice up to the renal pelvis. Subsequently, OCT images were acquired by retracting the imaging probe using an automatic pullback system at a pullback speed of 10 mm/s while rotationally acquiring 100 frames/s across a trajectory of 54 mm. This resulted in a 540-frame dataset in 5.4 s. After pullback, the imaging probe was manually repositioned at 50 mm distally in the ureter, and a new pullback was performed until the complete renal pelvis and ureter were visualized. After each pullback, the probe position was recorded using coregistered three-dimensional (3-D) CT.

2.2 Endoluminal Ultrasound Imaging

ELUS images were recorded using the Volcano Intravascular Ultrasound Imaging System interfaced to the Revolution® 45 MHz 3.5Fr (1.7 mm) intravascular ultrasound probe (Volcano Corporation, San Diego, California) with an axial resolution of 200 μm and a lateral resolution of 200 to 250 μm .¹⁰ Following introduction through the ureteral orifice, the imaging

probe was advanced into the renal pelvis. Subsequently, ELUS images were acquired by retracting the imaging probe using the Spinvision® automatic pullback system (Volcano Corporation, San Diego, California) at a pullback speed of 0.5 mm/s while rotationally acquiring 30 frames/s across a trajectory of 90 mm. This resulted in 5400-frame datasets obtained in 180 s. After each pullback, the imaging probe was manually repositioned at 80 mm distally in the ureter, and a new pullback was performed until the complete renal pelvis and ureter were visualized. After each pullback, the probe position was recorded using coregistered 3-D CT.

2.3 Computed Tomography Imaging

A Brilliance 64-slice CT scanner (Philips Medical System, Best, The Netherlands) was used to make CT scans of each of the nephroureterectomy specimens. The scans were made at a tube voltage of 120 kV and tube charge of 22 mAs. The total detector collimation was 64 × 0.625 mm. The filter used in the CT reconstruction was a medium smooth filter (filter B) and the final voxel spacing was 0.4 × 0.4 × 0.7 mm.

2.4 Image Reconstruction, Three-Dimensional Rendering, and Deformable Manual Computed Tomography-Based Coregistration

CT datasets (DICOM) each depicting a different OCT or ELUS probe position were loaded into the 3-D visualization software. An AMIRA embedded, automatic, rigid coregistration algorithm was used to accurately align the datasets in three dimensions. For separate depiction of (1) the probe, (2) kidney and ureter, and (3) perirenal fat, Hounsfield value-based automatic segmentations were performed on the CT data.

Subsequently, corresponding OCT and ELUS datasets (TIFF stacks) were loaded, displayed as 3-D-volume reconstruction, and visually aligned to the probe position as seen on CT, using the probe tip as the dataset’s starting point. Rotational orientation of the OCT/ELUS datasets was determined based on mutual visible image features in both imaging modalities, such as lumen contour and air bubbles. To correct for the curvature of the probe (and ureter) and to facilitate registration with pathologic slides, manual 3-D deformation of the OCT/ELUS datasets was performed. For this reason, the individual OCT/ELUS datasets were separated into 50-frame segments and manually aligned perpendicular to the CT-based probe segmentation in three dimensions. After alignment of the individual segments, recombination of the segments into a new, 3-D deformed dataset was conducted. This process was repeated for all datasets to aim for a virtually complete 3-D reconstruction of the ureter based on OCT and ELUS data only.

2.5 Pathology Preparation

The standard pathological report of nephroureterectomy specimens was considered the reference standard for comparison with OCT/ELUS imaging. Nephroureterectomy specimens dissected and examined at the pathology department according to a standardized protocol.

2.6 Image Analysis and Matching with Pathology

OCT and ELUS datasets were reviewed slice by slice for identification of ureter wall architecture, focusing on identification of ureter wall layers consisting of urothelium, lamina propria,

Table 2 Patient characteristics.

N	Gender	Age (year)	Tumor stage	Tumor grade	Tumor location
1	F	84	T1	2 (high grade)	Renal pelvis
2	F	48	Ta	2 (low grade)	Distal ureter
3	F	65	T1	3	Renal pelvis
4	M	74	T2	3	Renal pelvis
5	M	76	T1	3	Distal and proximal ureter, renal pelvis

muscularis propria, and periureteral fat. Ureteral abnormalities were defined as visible lesions and divided in noninvasive tumors or invasive tumors. Noninvasive tumors were defined as lesions. Images were scored inconclusive when imaged lesion transcended the field of view. Matching of histopathology with the corresponding regions of OCT/ELUS was achieved based on available histopathology slides with sufficient ureter tumor architecture and information provided by the uropathologist.

3 Results

Specimen characteristics are listed in Table 2.

All the patients underwent a diagnostic URS, including biopsies before radical nephroureterectomy. None of the patients received neoadjuvant therapy.

3.1 Computed Tomography-Based Coregistration

CT-based coregistration of ELUS and OCT data was achieved for five patients. Figure 2 shows an exemplary semitransparent 3-D rendering of the CT dataset, which was used for colocalization of the OCT and CT datasets. Within the CT rendering, a nontransparent purple probe has been made visible. The purple probe was automatically segmented based on Hounsfield units. The curvature of the probe was used to manually deform the OCT and ELUS datasets as shown in Fig. 3. A longitudinal cross section of both the OCT and ELUS dataset shows a clear difference in imaging depth. Additional visible markers such as the indentation caused by surgical clip, which was placed intra-operatively and was removed before introducing the imaging probes, show the accurateness of dataset matching.

3.2 OCT and ELUS Imaging of the Upper Urinary Tract

In OCT images of normal-appearing renal pelvis and ureter, the urothelium, lamina propria, and muscularis propria were clearly visible. In ELUS images of normal-appearing ureter, anatomical layers could be distinguished, although the resolution was lower compared to OCT images, and because of this low-resolution imaging, the urothelial layer could not be identified (Table 3). In OCT images with visible lesions, the anatomical layers could not be identified in all OCT datasets, resulting in a total identification of the urothelium in 79.4%, lamina propria in 79.4%, muscularis propria in 82.4%, and periureteral fat in 50% of the total OCT datasets (Table 3). In ELUS images, the inner mucosal layer is seen as a hyperechoic layer and recognized in 80.9% of the ELUS datasets. The muscularis layer is

Fig. 2 Coregistration steps as executed in AMIRA: (a) create and visualize segmented centerline of OCT probe in CT data, (b) read in OCT volume, (c) split total bounding box volume into 10 bounding boxes, (d) manually place individual OCT bounding boxes perpendicular to centerline probe in Y, Z plane, (e) manually rotate each individual OCT bounding box in X, Y plane to fit inner ureter shape, (f) and (g) merge individual OCT bounding boxes, and (h) visualize fused OCT-CT dataset.

Fig. 3 CT allowed coregistration and manual 3-D deformation of OCT and ELUS datasets to produce an integrated ureter volume reconstruction. Green arrows: radio markers in OCT probe and ELUS imaging probe. Blue arrow: notch caused by surgical clip that was placed intraoperatively and was removed before introducing the imaging probes. White arrowheads: papillary tumor seen in sagittal OCT and ELUS images.

hypoechoic and seen in 80.9% of the ELUS datasets, and the periureteric fat is hyperechoic and recognized in 80.9% of the ELUS datasets.

In the OCT imaging datasets, the urothelial layer is seen as a low-scattering layer and can be differentiated from the lamina propria, which is seen as a high-scattering layer. The muscularis layer is seen as a low-scattering layer. In the first case (Fig. 4),

Table 3 Results OCT versus ELUS.		
	OCT	ELUS
Urothelium (%)	80 (27/34)	0 (0/21)
Lamina propria (%)	80 (27/34)	81 (17/21)
Muscularis propria (%)	82 (28/34)	81 (17/21)
Periureteral fat (%)	50 (17/34)	81 (17/21)
Maximal imaging depth in lesions (mm)	2.0	3.5 ^a

Note: Results of OCT versus ELUS in the datasets.
^aMaximal imaging depth in lesions of ELUS is ~3.5 mm due to field-of-view settings. The maximal imaging depth of the ELUS imaging probe used in this study is 20 mm.

von Brunn’s nest could be seen in the lamina propria as a low-scattering spots within the high-scattering lamina propria layer. In ELUS images, the muscularis layer was identified as a hypoechoic layer surrounded by the hyperechoic periureteric fat as demonstrated in the first case (Fig. 4).

In both OCT images and ELUS images of suspected areas, lesions could be identified. The OCT imaging depth range is 2 mm where the ELUS maximum imaging depth in lesions is 3.5 mm. This maximum imaging depth of ELUS images was limited by the field-of-view standard and not by loss of imaging signal in the lesions. In specimens 2 and 3, tumor growth exceeded the OCT 2-mm imaging depth range and assessment of tumor invasiveness was hampered (Fig. 4). In the OCT image of case 2, a papillary structure is recognized. However, the lesion transcends the OCT imaging depth making accurate staging unreliable. Histology diagnosed a TaG2 urothelial carcinoma. In the OCT images of case 3, the tumor is seen as a high-scattering lesion that transcends the imaging depth. For this reason, no reliable staging can be assessed, although the image is suspicious for invasion. In the fourth case, high-resolution OCT images depicted clearly an invasive tumor. Invasion can be recognized as loss of architecture of the underlying layers. In the fifth case, invasive carcinoma was seen as a lesion with loss of architecture

Fig. 4 Cross-sectional images of the ureter and pyelum using ELUS, OCT, and matching histological images (10x hematoxylin and eosine staining). Case 1 demonstrates a normal-appearing part of the ureter. In the ELUS image, the hyperechoic inner mucosal layer (#), hypoechoic muscularis layer (§), and hyperechoic periureteric fat is shown (*). The probe is marked as *. The matching OCT image, thin urothelial layer (#), lamina propria (§) and muscularis propria (§) can be identified. Von Brunn's nests are recognized (arrowhead) and vessels (thick arrow). In cases 2, 3, 4, and 5, tumors are recognized as papillary (case 2) or solid lesions (cases 3, 4, and 5) (arrowheads). Architecture loss is seen in invasive tumors (cases 3, 4, and 5). In case 5, a nephrostomy tube was recognized in both images (thin arrow).

of the underlying layers. In this case, invasive carcinoma with a circular growth pattern was found in almost the complete resected specimen. For this reason, only in two of the eight OCT datasets anatomical layers were recognized. In ELUS imaging in cases 2, 3, 4, and 5, tumors are recognized as papillary (case 2) or solid lesions (cases 3, 4, and 5). Architecture loss is seen in invasive tumors (cases 3, 4, and 5), but exact staging and differentiation between noninvasive (Ta) and invasive ($\geq T1$) lesions were not possible due to low-resolution images (Fig. 4). In the OCT dataset of the pyelum, a nephrostomy tube was recognized. In the OCT imaging datasets, tumor invasion could not be assessed in two of the five patients because tumor thickness hampered OCT interpretation. Tumor thickness up to ~ 2 mm could be reliably assessed with OCT (Table 3). In our ELUS imaging datasets, exact staging was not possible, due to the increased imaging depth. However, ELUS provided a better overview of the lesions compared to OCT.

4 Discussion

This paper demonstrates the first results of one-to-one comparison of ELUS and OCT data of the human ureter. It shows that OCT permits high-resolution imaging of the upper urinary tract and UUT-UC whereas ELUS provides more depth information. These results warrant hardware integration of both technologies to optimize the diagnosis of UUT-UC.

The combination of OCT and ELUS allows for high-resolution imaging and greater imaging depth at the same time. This study demonstrates the potential of coregistered OCT and ELUS to visualize anatomical layers of the human upper urinary tract and the potential to discriminate between normal and suspected areas in an *ex-vivo* setting. However, the greater imaging depth obtained using ELUS did not result in improved staging of UUT-UC, since the imaging resolution of ELUS is too low to render reliable staging.

4.1 Optical Coherence Tomography of the Upper Urinary Tract

This study has shown that visualization of the urothelium, lamina propria, and muscularis propria is feasible with OCT in normal-appearing tissue. The imaging depth of ~ 2 mm even allows imaging into the periureteral fat layer. However, the imaging depth is a clear limitation when assessing a papillary lesion, impeding visualization of the lesion base and underlying layers, which is needed for an accurate estimation of tumor invasiveness. The ability of OCT to distinguish the different anatomical layers of porcine and human ureter has been demonstrated,^{4,11} and the potential to qualitatively differentiate between noninvasive and invasive UUT-UC has also been shown.^{4,12} This gives OCT the potential to stage UUT-UC. In addition, OCT has the potential to grade UUT-UC by quantification of the optical attenuation coefficient (μ_{oct}).^{4,12–16} Malignant tissue manifests as an increased amount of mitochondria and an increased nuclear/cytoplasm ratio. As a result, malignant tissue has different scattering properties compared to benign tissue, allowing visible lesions to be graded in OCT images by analyzing the decay of light in tissue expressed as μ_{oct} .

Although OCT could be used for staging of small lesions, large lesions exceeded OCT imaging depth range, making staging not possible for lesions larger than ~ 2 mm in depth. Merging OCT with an imaging modality with a larger imaging depth range overcomes this important limitation of OCT while the ability of OCT to grade lesions remains.

4.2 Endoluminal Ultrasound in the Upper Urinary Tract

Visualizing the mucosal layer, consisting of sublayers of urothelium and lamina propria, is possible with ELUS. However, differentiation of these sublayers is impossible due to a lack of contrast and low resolution. The 20-mm imaging depth allows the estimation of tumor size, although clear differentiation between noninvasive and invasive tumors cannot be achieved as a result of the limited resolution of $\sim 100 \mu\text{m}$. Nonetheless, it is the deeper penetration depth of ELUS that makes this technique interesting for endourological applications. For example, an advantage of larger imaging depth is the ability to determine the relation of specific pathology with its direct surroundings, such as lymphadenopathy in malignancy.¹⁷ Advances of ELUS have led to small catheter-based ultrasound probes allowing visualization of a variety of luminal structures.¹⁸ In the ureter, ELUS is

mainly used in the diagnostic work-up of stenosis of the ureteropelvic junction and its relation with intersecting vessels. However, a wide pathologic variety can be seen in the ureter, such as upper urinary tract tumors and endometriosis.^{17,19,20}

ELUS is based on the detection of the time delay in high-frequency sound waves, which are backscattered by tissue structures. The difference in resolution between OCT and ELUS is explained by the different wavelengths at which they operate. Unlike light waves in OCT, the transmission of sound waves needs a conduction medium, which is provided by the fluid present in the upper urinary tract lumen. A disadvantage of ELUS is the time needed for data acquisition, which is a factor 20 times longer compared to data acquisition using OCT. This increased acquisition time makes ELUS more sensitive to movements, resulting in blurred images. In an *in-vivo* setting, motion artifacts will occur due to ureteric peristalsis, breathing, and movement at the point where the ureter intersects with the great vessels. A second limitation of ELUS is its sensitivity for air bubbles.

This study shows data of OCT and ELUS acquired from the renal pelvis and ureter. Maneuvering the probe toward a suspected lesion in the renal pelvis compared to the ureter is more challenging but achievable after training of handling the imaging probe. Application of OCT and ELUS in the renal pelvis has been shown in previous studies as well.^{4,12,20}

4.3 Computed Tomography as a Guide for Probe Localization

The main challenge in coregistration of endoluminal imaging techniques is comparative localization with respect to histopathology. Coregistered ELUS and OCT combine greater depth imaging with superficial high-resolution images. To prove this, accurate correlation with histopathology is needed. To ensure that histopathology was obtained from the same location as OCT and ELUS measurements, accurate knowledge of probe position is needed. Therefore, we used CT to obtain reliable information on the intraureteral probe position correlated to overall anatomy.

4.4 Fusion of OCT and ELUS

To obtain reliable coregistration of OCT and ELUS, both diagnostic tools should have the same voxel size. This will result in accurate fusion of image features and measurement of layer thickness. However, optimal merging of OCT with ELUS needs parallel imaging instead of serial imaging. Several research groups have worked on integration of both imaging modalities resulting in a single hybrid catheter. Using this hybrid catheter, one-to-one acquisition of integrated OCT and ELUS images was obtained of coronary vessels.^{21–23} But standard OCT and ELUS acquisition do not take into account the curvature of the catheter in relation to the imaged lumen. A normal 3-D OCT or ELUS dataset is, therefore, usually depicted as a rigid tube. Several research groups have shown the possibility to fuse 3-D ELUS with CT. Centerline registration of the lumen found in CT data was employed to deform the rigid ELUS data in three dimensions, resulting in a more anatomically correct representation.^{22,24,25} Sharp curvatures, however, resulted in imperfect two-dimensional image spacing within a 3-D volume and should be taken into consideration during deformed 3-D reconstruction and coregistration. This is especially important when this technology will be applied *in-vivo*. For example, to

examine the lower pole calyces during a URS, the ureterorenoscope has to make a curve of almost 180 deg. Therefore, OCT and ELUS data acquisition should take this into account to provide the urologist with a reliable and realistic 3-D representation of the ureter, pyelum, and calyces.

5 Conclusion

In this pilot study, it appears that coregistration with CT enables exact spatial OCT and ELUS data matching in this *ex-vivo* setting. OCT permits high-resolution imaging whereas ELUS provides more depth information of the upper urinary tract. These results warrant hardware integration of both technologies to combine larger depth sensitivity with superficial high-resolution images. However, differentiation between noninvasive and invasive tumors is not possible using the 45-MHz ELUS system employed in this study due to low-resolution images.

Disclosures

The authors no relevant financial interests in this paper.

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Mieke T. J. Bus is a resident in urology at the OLVG Amsterdam and has a great interest in upper urinary tract urothelial carcinoma, especially in improving diagnostic techniques for upper urinary tract urothelial carcinoma. The past years she has written multiple publications on this and other topics in the urological field and is currently finishing her PhD at the Academic Medical Center Amsterdam.

Biographies for the authors are not available.