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Are we closer to seeing carcinoma *in situ* in the upper urinary tract?

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Introduction There is observed increase in detection rate of upper urinary tract urothelial cancer worldwide. This is a result of improved imaging as well as implementation of novel technologies of direct visualization of upper urinary tract. Standard techniques still remain insufficient to diagnose flat urothelial lesions. Carcinoma *in situ* is characterized by flat disordered proliferation of urothelial cells with marked cytologic abnormality, which occur within one cell layer as well as full thickness urothelium and therefore requires a better technology to pick up early and subtle mucosal changes.

Material and methods The review presents available diagnostic tools in detection of upper urinary tract urothelial cancer and their ability to depict carcinoma *in situ*.

Results Ureterorenoscopy is an investigation of choice as various promising techniques are under pilot investigations to enhance visualization of upper urinary tract carcinoma *in situ.* So far only photodynamic diagnosis has been reported to be as effective in detection of carcinoma *in situ* in the upper as within the lower urinary tract.

Conclusions Although we are close to see upper urinary tract carcinoma *in situ* all new promising diagnostic techniques still require further validation in multicenter clinical trials to indicate any change to current recommendations.

Key Words: upper urinary tract ‹› urothelial cancer ‹› carcinoma *in situ* ‹› detection

INTRODUCTION

Although carcinoma *in situ* (CIS) is classified as non-muscle invasive urothelial cancer, its natural history shows a high potential of progression to muscle invasive cancer. Sharma et al. reported the inability and difficulty to diagnose and eradicate upper urinary tract carcinoma *in situ* (UUT-CIS) [1].

Although UUT-CIS is rare, there has been an increase in its detection rate recently. Karam et al. reported a 2% incidence of primary UUT-CIS following a review of 1364 nephroureterectomy specimens [2]. The incidence of primary UUT-CIS was higher (11%) in a UC-UUT Spanish Collaborative Group multicentre retrospective database during the period 1950–2010 [3]. UUT-CIS concomitant to either lower or upper urinary tract urothelial cancer appears to be diagnosed more often. Wheat et al. reported concomitant CIS in 26.7% of nephroureterectomy specimens performed [4] and CIS was confirmed in the distal ureter in 25% of patients having undergone radical cystectomy [5]. Lopez-Beltran et al. found that patients receiving BCG (Bacillus Calmette-Guerin vaccine) intravesical treatment, who remained recurrence-free in the bladder, were at higher risk of developing UUT-CIS [6]. Giannarini et al. suggested investigating the upper urinary tract (UUT) for missed CIS in all patients who failed BCG treatment of the bladder, as UUT lesions could be detected in more than 50% of cases [7]. This recommendation was supported by the National Comprehensive Network Guidelines on Bladder Cancer [8].

An early diagnosis is crucial as CIS is the most important predictor of UUT urothelial cancer (UUT-UC)

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recurrence and cancer specific mortality for organ-confined disease. There is therefore an urge to establish an effective diagnostic tool. The aim of this review is to depict the most effective amongst available diagnostic tools for the detection of UUT-CIS.

Imaging

Multidetector Computerised Tomography Urography (MDCTU) is the radiological gold standard for the detection of UUT-UC. Although the technique is characterised by high sensitivity (67–100%) and specificity (93–99%), flat lesions are undetectable until they have progressed to thickening of the upper urinary tract wall [9]. Caolili and Li-Jen reported CIS to be invisible on MDCTU [10, 11]. Jinizaki noted UUT-CIS in two of three false negative results in a comparative study of CT urography and excretory urography [12].

Magnetic resonance remains an alternative in patients who are not suitable for MDCTU [13]. Nishizawa evaluated diffusion-weighted (DWI) magnetic resonance imaging (MRI) in detection of UUT-UC. The sensitivity was 94.1% for DWI and 76.5% for standard MRI, but neither modality was able to depict primary as well as concomitant CIS [14]. Sufana Iancu reported similar results for CIS and small UUT-UC [15].

Imaging provides minimal information and therefore an early detection of flat UUT-UC (including CIS) requires combined multimodal investigations [16].

Cytology

A cytology test of urine sampled from the bladder is of little value in the detection of UUT-UC (including CIS). In contrast, the cytological assessment of urine from the upper urinary tract (barbotage) is a first-line investigation, which follows negative / equivocal imaging in suggesting possible CIS. Wang et al. reported sensitivities for biopsy specimen, lower urinary tract cytology and upper urinary tract cytology to be 82.9%, 40.7%, and 80.6% respectively [17]. Chen et al. found the specificity and negative predictive value of urine cytology from the upper urinary tract (barbotage) for high-grade urothelial cancer to be 91.9% and 93.4% respectively [18]. Unfortunately, positive cytology cannot localise CIS, but indicates direct visualisation of the UUT. High specificity of cytology for high-grade urothelial cancer suggests the significant role of brush cytology in the mapping of UUT. Dodd analysed 63 brushes from UUT and compared them with washout and pathology specimens from standard biopsies. He concluded that brush cytology was not successful in detection of CIS [19].

Fluorescence *in situ* hybridisation (FISH)

FISH is a urinary test containing cystometric probes for chromosomes 3, 7 and 17, and a locus specific probe for chromosome 9p21, which aims to detect chromosomal abnormalities typical of urothelial cancer of the bladder. UroVysion appears to have the highest sensitivity. FISH appears to be more accurate than urinary cytology. Caraway et al. reported sensitivity and specificity to be 58% and 66% respectively for UroVysion alone and 59% and 63% respectively for UroVysion combined with cytological examination. Negative and positive predictive values of FISH were 79% and 42% respectively [20]. FISH is not specific for urothelial cancer and can return positive results for renal cell cancer as well. Johannes et al analysed the usefulness of FISH in detection of UUT-UC. They assessed high- and low-grade lesions. They found sensitivity for all UUT-UC to be 54%, with a specificity of 78%. They also reported false negative rate of 46%. Surprisingly, FISH was more sensitive for low-grade (60%) than high-grade (50%) UUT-UC [21]. FISH offers limited value in the detection and surveillance of UUT-CIS [9]. Other tests like ImmunoCyt and BTA Stat have been reported to be poor at identifying UUT-UC thus far.

Endoscopy

UUT-CIS mirrors CIS of the bladder [22]. Standard white light ureterorenoscopy remains a poor diagnostic tool and akin to cystoscopy requires an invasive approach with increasing number of tissue samples taken to improve detection rate of CIS [23]. Sensitivity of multiple bladder biopsies is around 77% [24]. Multiple random biopsies are, however, of minimal value in detection of CIS, as benign reports are not reliable [25]. Although the multi-biopsy protocol appears to improve detection of UUT-UC [26], this does not work for CIS. The SUTURE group, having analysed the results of ureterorenoscopy performed prior to nephroureterectomy, found that white light endoscopy missed 84.7% of CIS lesions [27]. Yamany et al. reported 44% and 56 % of CIS lesions missed in the ureter and pelvicalyceal system respectively on pre-nephroureterectomy ureterorenoscopy. CIS represented 50% of lesions, which were not depicted by white light ureterorenoscopy [28]. CIS can present as a microscopic focus within the upper urinary tract and therefore there is a risk of missing it even on pathological examination of a post-nephroureterectomy specimen. Gillan et al. noted that six out of 10 patients with CIS on ureterorenoscopic biopsies had no CIS on a final histopathological report of the nephroureterectomy specimen [27].

Optical diagnostic techniques

Various technologies have been implemented to improve visualisation of UUT-CIS [29]. Narrow band imaging (NBI) is a high-resolution technique using different light wavelength penetration into tissue. It is based on blue (superficial penetration) and red (deeper penetration) excitation of urothelium. The blood is a strong absorber in the red / near infrared light; therefore NBI improves visualisation of blood vessels. In 2011, Traxer suggested a 22.7% improvement in the detection rate of UUT-UC by adding NBI to white light ureterorenoscopy, but there has been nothing reported of its value in depicting CIS in the upper urinary tract as of yet [30].
The Storz professional image enhancement system (SPIES) is another promising technology. The technique is based on a full high-definition image processed by enhancement software improving brightness (CLARA), colour contrast (CHROMA) and assessment of tissue structure (SPECTRA A, B). The results of the Clinical Research Office of the Endourological Society (CROES) study assessing SPIES visualisation of UUT lesion including CIS are awaited.
Pilot studies suggested the feasibility of optical coherence tomography (OCT) to confirm CIS within UUT during real-time ureterorenoscopy [31]. This interferometric technique analyses reflection of light from mucosal and submucosal layers giving high-resolution 3D pictures of urothelial microarchitecture with live assessment similar to pathological examination. Clinical trials are still awaited.
Confocal laser endomicroscopy (CLE) enhances images obtained by conventional microscopy through better depth of resolution and therefore allows assessment of urothelial superficial layers following light excitation of the photosensitizer. Pilot studies with the Cellvizio probe and 10% fluorescein (photosensitizer) confirmed the ability to define tissue architecture within UUT and depict low- and high-grade urothelial cancer [32, 33]. CLE was able to differentiate cancerous from inflammatory tissue [34]. This is very promising, as inflamed urothelium appears quite similar to CIS. Although pilot studies suggest the ability to visualise high-grade UUT-UC, there has been no data regarding the detection of CIS. Furthermore, neither OCT nor CLE allow wide-field scanning, and thus require guidance by other techniques, which does not favour the depiction of all multifocal CIS lesions.
Photodynamic diagnosis (PDD) appears to be the most effective and recommended technique to enhance visualisation of CIS in the bladder. Kausch et al. reported an additional detection rate of 39% for CIS in a meta-analysis of seven studies that specifically reported on CIS [35]. The most recent report of 106 photodynamic diagnostic ureterorenoscopies (PDD-FURS) with oral 5-Aminolevulinic acid (5-ALA), as a photosensitizer, suggested significant improvement in the detection rate of UUT-CIS lesions. Total tumour detection rate for PDD-FURS was 95.8% with a reported rate of 47.9% for white light ureterorenoscopy (WL-FURS). This concurs with previously reported findings in the bladder. PDD-FURS was superior to white light for CIS / dysplastic lesions, with a detection rate of 93.75% *versus* 18.75% [36]. The ability to detect dysplasia is of great clinical significance as it can coincide with primary UUT-CIS [37]. In a pilot study, Agrawal suggested the ability of PDD-FURS to visualise UUT-CIS (2 of 5 lesions missed under white light) following retrograde instillation of hexaminolevulinate hydrochloride (Hexvix) into the upper urinary tract and bladder [38]. CIS is multifocal panurothelial lesion. Systemic (oral) administration of 5-ALA is a much easier technique of simultaneous assessment of the lower and upper urinary tracts; therefore, it seems to be an ideal technique for screening of CIS lesions. The detection rate of CIS in the bladder during PDD-FURS was 8.3% for white light and 91.7% for blue light.
Extensive denudation of urothelium is a significant risk factor for generation of false negative biopsies. Marked red fluorescence from CIS within UUT allows visualisation of denuded CIS, as well as confirms its presence in biopsy forceps (targeted biopsy) [36].

Summary

Current imaging does not support visualisation of flat UC or CIS/dysplastic lesions, therefore not favouring nephron-preserving treatment, in addition to negatively impacting surveillance following extirpative procedures. The diagnostic decision still relies on CT / MRI negative findings and does not routinely escalate endoscopic panurothelial visualisation should the urinary cytology test be abnormal. Detection value of urinary cytology, FISH and other molecular diagnostic tests remains low and all tests can only be used as screening modality. As a consequence, diagnosis of UUT-CIS is always delayed.
We have started seeing CIS lesions within the upper urinary tract. Promising endoscopic techniques have emerged due to the advances of flexible ureterorenoscopes combined with modern optical diagnostic techniques. Although most are under evaluation, recent publications suggest a high detection rate of UUT-CIS by photodynamic diagnosis, which allows simutaneous assessment of lower and upper urinary tract (bilateral should be required). The technique

can shed more light on the natural history of CIS and may lead to organ-preserving treatment within the upper urinary tract. Very accurate visualisation opens a new, promising avenue to direct ablative endoscopic treatment, which can be combined with adjuvant BCG instillations. Kojima suggested BCG instillation to be as effective as nephroureterectomy for UUT-CIS [39]. Giannarini published promising results of curative adjuvant instillations following endoscopic ablation of CIS compared to pTa/pT1 urothelial cancer [40].

CONCLUSIONS

Difficulty in visualisation of UUT-Cis does not favour any attempts of ablative treatment and therefore nephroureterectomy remains the undisputable gold standard. Urine cytology remains more accurate than imaging in suggesting Cis, but direct panurothelial visualisation of the urinary tract does not follow normal imaging routinely. Ureterorenoscopy may be the test of choice as various promising techniques are under pilot investigations to enhance visualisation of UUT-CIS. So far only photodynamic diagnosis has been reported to be as effective in detection of UUT-CIS as within the lower urinary tract. A high detection rate may warrant better understanding of the natural history of the disease. One can hypothesize that exact direct visualisation may improve outcomes of ablative therapy to eradicate UUT-CIS and adjuvant topical treatment to remaining urothelium in the future. Although we are close to seeing UUT-CIS all new promising diagnostic techniques still require further validation in multicentre clinical trials to indicate any change to current recommendations.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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