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ORIGINAL ARTICLE

Multidetector Computed Tomographic Urography (MDCTU): Its Practical Role in Diagnosis of Upper Tract Urothelial Cancer in Patients 50 years and Older with Different Types of Hematuria

Sergey Kravchick[1,2] · Eugenia Cherniavsky[3] · Guy Verchovsky[1] · Ronit Peled[4]

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Abstract MDCTU is a preferred method for the investigation of malignant lesions in the upper urinary tract. However, to decrease unnecessary radiation exposure the indications for the exam in different groups of patients should be assessed. In this study, we evaluated the role of MDCTU in patients older than 50 years who presented with different types of hematuria. In a retrospective manner, we assessed the radiologic reports of 173 patients ≥50 years who underwent MDCTU as a part of the evaluation for hematuria. To estimate the accuracy of MDCTU in the detection of upper urinary tract urothelial carcinoma (UUTUC) we compared MDCTU findings with the results of ureteroscopy. We also evaluated which factors can predict ureteroscopic confirmation of MDCTU-based diagnosis. In this list we also included diabetes mellitus and anticoagulant medications. As a result, 140 (103 males and 37 females) patients met the inclusion criteria. Mean patients' age was 69.7±16.98. Smokers and passive smokers comprised 38.6% and 26.4% of our patients, while 37.8% of our patients suffered from DM and 45% took anticoagulant medications. MDCTU suspected urothelial carcinoma in 17% (n=24) of our patients: UUTUC in eight and bladder urothelial carcinoma (BUC) in 16patients. Ureteroscopy had diagnosed UUTUC (with/without concurrent urothelial carcinoma of the bladder) in 9 patients: 6 with suspicious lesions in MDCTU and 3 additional patients with CIS/small low grade TCC. MDCTU had a sensitivity of 66.7%, specificity - 98.5%, positive predictive value - 75% and negative predictive value - 97.7%. The logistic regression model revealed five strong predictors for UUTUC: positive/atypical cytology, recurrent hematuria, MDCTU signs, age and Warfarin treatment. Finally a source of hematuria was diagnosed in 57% of patients, while MDCTU individual accuracy reached 42%. We found that MDCTU can effectively identify patients in whom further endoscopy is unnecessary. Otherwise, elder patients with positive/atypical cytology and recurrent microscopic hematuria, who have MDCTU signs and take Warfarin, should undergo endoscopic evaluation.

Keywords Upper tract TCC · Computer tomography · Urography · Hematuria · Ureteroscopy

✉ Sergey Kravchick
kravchick.sergey@gmail.com

[1] Present address: Department of Urology, Assaf Harofeh Medical Center, Zrefin, Israel

[2] Department of Urology, Barzilai Medical Center, Ashkelon, Israel

[3] Department of Roentgenology, Barzilai Medical Center, Ashkelon, Israel

[4] Epidemiology and Statistics, Ben Gurion University, Beersheba, Israel

Background

Urothelial carcinoma (UC) is the 4th – 5th most common malignancy [1, 2]. Most of these tumors are in the bladder (90–95%), however 5–10% of UC are detected in the upper urinary tract (UUT): pyelocaliceal cavities and ureter [3, 4]. The estimated annual incidence of the latter tumors in Western countries is about one to two new cases per 100,000 inhabitants, with pyelocaliceal tumors are about twice as common as ureteral [5]. It also must be reminded that recurrence of disease in the bladder occurs in 30–51% of patients with UUTUC, whereas a relapse in the contralateral upper tract are observed in 2–6% of the cases [6–8].

In most cases the diagnosis of UUTUC is a consequence of the investigation for hematuria [2]. It must be emphasized that a number of these tumors continue their growth

asymptomatically and without microscopic hematuria, thus nearly 60% of UUTUC are invasive at diagnosis [9]. For this reason, imaging plays one of the most important roles in diagnosis of UUTUC. Currently Multidetector Computed Tomographic Urography (MDCTU) became the gold standard for the UUT examination and had replaced intravenous excretory urography [10–12]. This method is very attractive as both the renal parenchyma and urothelium can be evaluated with one relatively noninvasive comprehensive exam [13, 14].

The Aims of the Survey

Previous studies tried to discover in which group of patients MDCTU might be the most efficient [15–19]. Based on the results of those studies, it could be presumed that the likelihood to detect of UC increases in patients ≥50-year-old who present with recurrent episodes of microhematuria or single event of gross hematuria. In this retrospective study, we attempted to assess the role of MDCTU in this group of patients, presented with different types of hematuria.

Materials and Methods

For the above-mentioned purpose, we evaluated MDCTU reports of 173 patients, presented with different types of hematuria (Fig. 1). In that period, we performed MDCTU in patients with macroscopic hematuria, microscopic hematuria (two consecutive urinalysis with ≥3 RBCs/high-power) and recurrent microscopic hematuria (the latter is defined as microscopic hematuria in at least two non-consecutive urinalysis during a one-year period). In our institution, we perform MDCTU before the consequent diagnostic procedure (Cytsoscopy and Ureteroscopy). This study was approved by the ethics committee of our hospital Board (BRZ-0081-12). Each patient gave written Informed Consent. Our inclusion criteria included consecutive cystoscopy and cytology in all patients ≥50 years, while ureteroscopy had to be done in cases of MDCTU suspected UUTUC and/or positive cytology with normal cystoscopy, as well as bleeding from ureteral orifice. Otherwise, patients with known UUTUC and patients in whom ultrasound exam revealed suspected solid lesions in kidneys' parenchyma were excluded from the study.

All MDCTU was done on a 16- or 64 scanners (Philips Healthcare). Our protocol incorporates a single-bolus technique, which was proven to provide optimal visualization of the collecting system and ureters and has greater sensitivity for small renal cell carcinomas (RCC) [20]. All patients were given 600 ml of water to drink 20 min before the exam and were placed in the supine position. Since MDCTU protocol is a triphasic examination, in the first phase we made unenhanced imaging from the top of the kidneys to below the symphysis, using 0.8–2.5 mm collimation. Second phase was performed 100 s after the IV injection of 100 ml non-ionic contrast (Iopamidol 300). Though some authors proposed to restrict delayed images to 5 min after contrast agent injection [20, 21], we found that in many cases it took more than 5 min to opacify the ureters. To overcome this problem, we preferred to start the excretory phase imaging 15 min after the contrast medium injection. At this point we turned the patient to the prone position to accelerate full distention of ureters. Senior radiologists reviewed all examinations, and the following roentgenological findings were interpreted as suspicious for UUTUC: soft tissue mass, ureteral wall thickening, urothelial enhancement and ureterohydronephrosis.

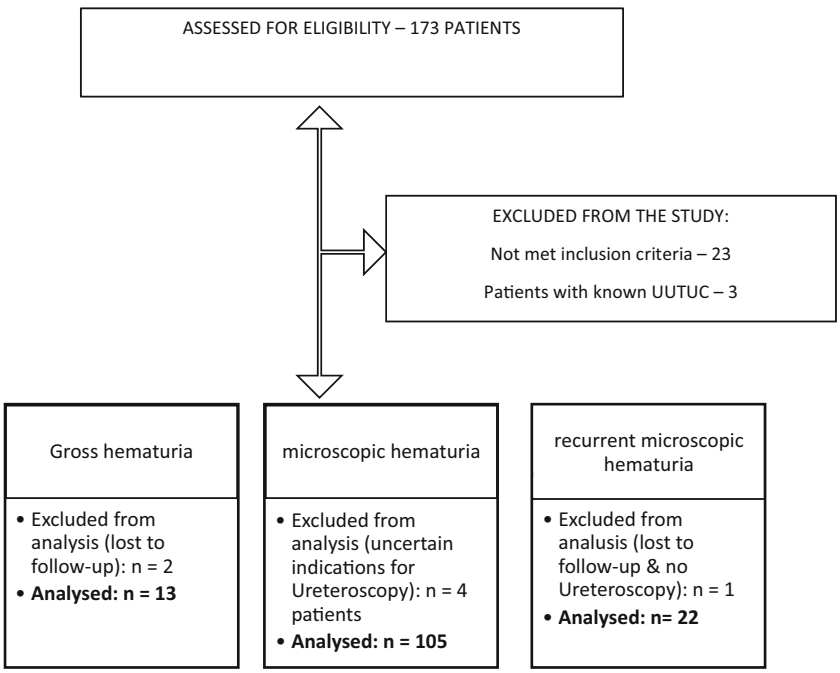

Fig. 1 Flow diagram of the study population: 140 patients included in final analysis

The final goal of this study was to estimate the accuracy of MDCTU in diagnosing UUTUC in adults ≥50 years presented with different types of hematuria. For this purpose, we compared MDCTU findings with the results of ureteroscopy. We also assessed a correlation of different MDCTU signs with clinical confirmed UUTUC. To optimize this task, we divided MDCTU reports for two groups: "one sign" – only one of the essential signs such as urothelial thickening or filling defect was detected; and "two signs" when both former sings or their combination with urothelial enhancement and/or ureterohydronephrosis were detected.

In addition, we tried to reveal in which particular group MDCTU might be the most useful and what factors can predict the accuracy of this exam. Accordingly, we assessed different parameters, such as age, gender, type of hematuria (macro-or microscopic/recurrent), presenting symptoms, occupational risk factors and urine cytology. Since previous studies have proposed an epidemiological role of diabetes mellitus (DM) in UC [22], we included DM in the list of risk factors. Likewise, we hypothesized that aspirin and warfarin may provoke bleeding from the highly vascularized areas of UC, rather than cause a non- specific bleeding. That is why we also touched on these factors as potential predictors.

We used logistic regression model in which ureteroscopic confirmation of UUTUC was considered as a dependent variable. Otherwise, several independent variables such as MDCTU signs, demographic data, smoking habits, occupational risk factors, DM and different types of hematuria were included in the model at distinct steps. Statistical software SPSS 15 was used for these purposes. We also calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for MDCTU in diagnosing UUTUC and Bladder Urothelial Cancer (BUC). Histologically proved UC on consecutive ureteroscopy and cystoscopy was considered as a true positive.

Results

Accordingly, 140 of 173 patients were included in this study (Fig. 1). Mean patients' age was 69.7 ± 16.98 and there were 103 males and 37 females. Overall cancer was detected in 26 patients: UUTUC – 9 and BUC −17. The lag between MDCTU and consecutive endoscopy was 5.3 ± 1.5 weeks. Smokers and passive smokers comprised 38.6% and 26.4% of our patients, while 37.8% of our patients suffered from DM, 28.6% were on the aspirin and 16.4% on the warfarin treatment. It must be emphasized that 32(22.9%) of our patients presented with hematuria plus lumbar pains and/or dysuria.

Based on the MDCTU reports UC was suspected in 24(17%) of our patients: UUTUC −8 and BUC 16 patients. In two of these patients both UUTUC and BUC were suspected. Among patients with suspected UUTUC five had one and three ≥2 roetgenologic signs. Ureteroscopy had diagnosed UUTUC in 9 patients (2 with concurrent BUC): 6 with suspicious lesions on MDCTU and 3 additional patients who underwent ureteroscopy for positive cytology/hematuria from ureteral orifice. Carcinoma in situ (CIS) of ureteral (n-2) and low-grade UC (n-1) were diagnosed in the latter patients. In 2 false diagnoses of UUTUC we detected ureteric cystica and necrotic tissue, consistent with diagnosis of papillary necrosis. As a result, MDCTU for UUTUC got a sensitivity of 66.7%, specificity - 98.5%, PPV - 75% and NPV - 97.7%. Logistic regression model revealed five strong predictors for UUTUC: positive/atypical cytology, recurrent microscopic hematuria, MDCTU signs, age and warfarin treatment.

Just 13 of 16 patients with BUC suspected on MDCTU, had clinical/pathological confirmation of malignant neoplastic disease. Consecutive cystoscopy detected BUC in 4 additional cases: 3 small volume, low grade/low stage UC and in one CIS. Thus, the diagnostic ability of MDCTU to detect and exclude BUC resulted in sensitivity of 76.5%, specificity – 97.6%, PPV – 81% and NPV – 96.7%.

Finally, a source of hematuria was diagnosed in 57% of the patients (MDCTU + ureteroscopy + cystoscopy), while MDCTU individual accuracy reached 42% (n-59). Except UUTUC and BUC, MDCTU accurately diagnosed 3 cases with RCC (Renal Cell Carcinoma) which were described by US as hyperdense cyst. Other main diagnoses included AML, renal cyst, nephro- and ureterolithiasis, BPH – 22.8% of the study population.

Discussions

Hematuria remains the most common presenting symptom of UC and UC prevalence among this patient typically ranges between 3% and 6% [16]. Consequently, it was proposed that all patients older than 40 years who present with hematuria should undergo MDCTU and cystoscopy, although the sensitivity and PPV of this workup resulted in a 50% 13%, respectively [2, 5, 15, 23]. Our study showed that recurrent microscopic hematuria became one of the strongest predictors for UUTUC. Indeed, 6 of 9 patients with UUTUC had recurrent microscopic hematuria (Table 1). Interestingly, in patients with BUC macroscopic hematuria played a key role. Therefore, we would like to support the role of compete evaluation with upper urinary tract imaging and cystoscopy in patients with *macroscopic* and *recurrent microscopic* hematuria Table 2.

The natural history of UUTUC differs from that of BUC, as nearly 60% of UUTUC are invasive at diagnosis and the mean age of occurrence is 65 years and older [24]. In this association, we would like to underline the facts that 25% of our This trend for occurrence in elder population was further assessed by Chlapoutakis et al. [14]. The authors found that *male gender, age > 50 years, and a previous history of gross hematuria*

Table 1 Types of hematuria in patients with UUTUC (Upper Urinary Tract Urothelial Carcinoma) and BUC (Bladder Urothelial Cancer)

Patients' study number	UTUC	BUC	Hematuria: microscopic	Hematuria: gross	Hematuria: recurrent	Walfarin treatment
1	+	–	+	–	–	–
4	+	–	+	–	+	+
7	+	+	+	+	+	+
11	+	–	–	+	–	–
17	–	+	+	–	–	–
22	–	+	+	–	–	–
23	+	+	+	–	+	–
31	–	+	+	+	+	+
35	–	+	+	–	–	–
47	–	+	+	–	+	+
54	–	+	+	–	–	–
59	–	+	–	+	–	–
62	+	–	+	–	+	–
65	+	–	+	–	–	–
73	–	+	–	+	+	+
85	–	+	+	–	–	–
92	–	+	–	+	–	–
93	+	–	+	–	+	–
101	–	+	+	–	–	–
105	–	+	–	+	–	+
111	+	–	+	–	+	+
127	–	+	–	+	–	–
133	–	+	+	–	–	–
140	–	+	–	+	–	+

were significantly associated with a higher chance to detect UUTUC. In this study, an indexation system was developed and resulted in cancer detection rate of 11.6% in the high-risk group. Consequently, authors concluded that patients <50 years without a history of gross hematuria could safely avoid evaluation with cystoscopy and MDCTU [14]. In this consent, we emphasize that nearly 25% of our patients presented with recurrent microscopic and/or gross hematuria, also, 74% of patients were males within are-range 69.7 ± 16.98 and nearly 65% were active or passive smokers, an additional risk factor for aggressive UC associated with a worse prognosis [25]. Consequently, the study population possesses features of a high-risk group and, as a result, the detection rate for UUTUC reached 6%, UUTUC + BUC 17% and for UUTUC + BUC+ Renal Cell Carcinoma (RCC) came to 19%. Accordingly, we proposed that MDCTU should be included in the evaluation of patients with recurrent microscopic/gross hematuria, who are ≥50 years-old and, especially, have a prolong history of active/passive smoking.

Table 2 Five strong predictor of UUTUC (Upper Urinary Tract Urothelial Carcinoma) detection

Dependent variable	B	S.E.	Wald	df	Sig.	Exp(B)
Positive cytology	3.734	0.726	26.469	1	**0.000**	41.834
Recurrent hematuria	1.443	0.546	6.981	1	**0.008**	4.233
CTU sign 1	2.771	1.044	7.046	1	**0.008**	15.980
CTU sign 2	3.312	1.415	5.480	1	**0.019**	27.428
Age	0.076	0.34	4.795	1	**0.029**	1.078
Warfarin	1.23	0.657	3.502	1	**0.037**	2.546
Gender	0.212	1.097	0.37	1	0.847	0.809
Smoking	0.276	1.142	0.058	1	0.809	1.317
Passive smoking	0.393	1.06	0.138	1	0.711	0.675
Occupational risk factors	1.473	1.623	0.824	1	0.364	0.229
DM	1.008	2.355	0.183	1	0.669	0.365

CTU sign 1 - only one of the essential signs such as urothelial thickening or filling defect was detected on MDCTU; CTU sign 2 - when both former sings or their combination with urothelial enhancement and/or ureterohydronephrosis were detected

DM, Diabetes Mellitus

Significance in Bold emphasize $p < 0.005$

In their previous study, Caoili et al. had found that irregular and eccentric urothelial thickening is the most common manifestation of UUTUC and a lesion <5 mm form a diagnostic threshold for MDCTU [26]. Other authors emphasized the significance of the endoluminal filling defect, focal or asymmetric urothelial enhancement on the arterial phase images and further recommended that even circumferential and smooth ureteral wall thickening should be looked upon with suspicion for UUTUC [27, 28]. Our study recognized that MDCTU signs constitute strong predictors for UUTUC. It must be underline that urothelial thickening and endoluminal filling defect along had very strong predictive power (0.001). In our study, the overall MDCTU sensitivity was lower, specificity nearly the same while PPV higher than that reported in the previous study [11]. This relative increase in PPV in our study may be explained with the certain points of our protocol: we usually perform the excretory phase imaging 15 min after the contrast medium injection and use prone positioning to get full opacification of the ureters and their full distention [20].

We also would like to highlight that our NPV was high and reached 97.7%. Summarizing the above statements, we hypothesize that high specificity and NPV of MDCTU helps to decide whether ureteroscopy should be managed or avoided.

It was specified in the previous studies that UC might be detected in only 0.43%–3.4% of patients presented with hematuria, in an additional 16.2%, 4.0%, 2.3%, and 0.9% it could be caused by nephrolithiasis, prostatic bleeding, urinary tract infections/glomerular disease while in 61%–77% its origin remains unknown [14, 29, 30]. The higher rate of UC in our study could be explained by the fact that the population of our study belongs to a high-risk group.

Some recent studies found that DM was associated with an increased risk of developing UC. It was proposed that DM may cause changes in urine composition and bladder function that could increase the concentration of carcinogens in the urine and consecutive prolong exposure of urothelium to these substances [22]. Although nearly 38% of our patients suffered from DM, in this study we failed to find significant association between DM and increased risk for UC. On the other hand, we found that warfarin had a strong predictive ability to detect UUTUC in patients with hematuria (p-0.037). 0.001).

Conclusion

MDCTU should be primarily performed in the patients >55 years, with recurrent microscopic or single episode of gross hematuria, especially in patients who take warfarin. Delate excretory phase imaging should be performed with patients turned to the prone position. Urothelial thickening and endoluminal filling defect along or in different combinations predict the presence of UUTUC. MDCTU results may be used to exclude the patients who do not need further ureteroscopy.

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