Role of dual source CT cistography and virtual cystoscopy in detection of bladder cancer: Comparison with photodynamic diagnosis (PDD) method in the bladder cancer

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Purpose

Flexible cystoscopy is the gold standard for diagnosing bladder cancer, not only because of its high sensitivity and specificity in detecting lesions but also the possibility of performing resections or biopsies in real time [1]. Despite the development of new cystoscopes and examination techniques,

flexible cystoscopy still remains an invasive investigation that is poorly tolerated by patients and is precluded in subjects with acute bleeding or urethral strictures [2]. To address these limitations, in 1996, Vining et al. introduced CTC with VC as a minimally invasive modality for the endoscopic study of the bladder and the detection of bladder lesions [7]. Only 1 year later, Hussain et al. [9] suggested replacing conventional cystoscopy with VC as a first-line diagnostic approach in patients with hematuria or for the follow-up after tumor resection. The technique has undergone extensive development, and recent studies [10-12] have demonstrated its high sensitivity for bladder cancers. Today, thanks to the widespread availability of multidetector CT scanners, CTC with VC is no longer regarded as a sophisticated technical development but, like virtual colonoscopy in the past, is slowly being incorporated into routine clinical practice. With regard to lesion size, it has been also demonstrate that multidetector [13] CT performed with thin-slice reconstructions (1 mm)[14] allow a good sensitivity in the detection of lesion over 1 mm. The use of MDCT with Dual Source technology should improve z-axis resolution and increase spatial resolution, thanks to the acquisition of isotropic voxels, such that excellent sensitivity and specificity can be obtained for very small lesions. The aim of this study is to evaluate the role of CTC and Virtual Cystoscopy with Dual Source technique in detection of bladder lesions using Cystoscopy with Photodynamic Diagnosis (PDDs) as reference standard.
Methods and Materials

Study population between January 2008 and October 2009, we selected 44 patients referred to the urinary cancer clinic of our Institution. The population was initially divided into 30 patients who had not undergone surgery and fourteen patients who were being followed up after transurethral resection of the bladder (TURB). All patients had a medical history suspicious for bladder cancer, including hematuria with negative urine culture, exposure to carcinogenic chemical agents, family history, recurrent or parasitic infections and positive cytology on urinalysis. The patients being followed up after TURB underwent routine laboratory tests with cytological examination. All 44 patients underwent sovrapubic and transrectal ultrasonography with bladder-wall assessment and post-voiding urine volume. At the time of the CT study, the study population ranged in age from 50 to 77 years. Approximately 1 week after the CT scan, each patient was studied with conventional cystoscopy or with Cystoscopy with Photodynamic Diagnosis (PDDs) to determine the presence, location, morphology and size of any bladder lesions, including flat lesions and Cis (Carcinoma in situ). Lesions were resected and the specimens sent to the pathology laboratory for histological typing. All patients gave their informed consent, as required for approval by the institutional ethics committee and inclusion in the study protocol.

Patient preparation

Before CT examination, a three-way 12-F Foley catheter was inserted into the bladder to achieve complete voiding. The bladder was then distended by insufflating 350-500 cc of room air with 50 cc syringes, depending on patient tolerance. No spasmyloytic agents were administered during bladder distension. Following the examination and catheter removal, all patients were prescribed a 3-day course of prophylactic antibiotic therapy.

Photodynamic Diagnosis (PDDs) Cystoscopy

Involves fluorescence to localize abnormal tissue. In urology, clinical interest in PDD mainly has focused on the improved detection of hardly visible urothelial bladder cancer. Small papillary tumors and flat urothelial lesions can easily be overlooked during conventional white light cystoscopy. Preventing correct and early treatment, missed diagnosis of high-grade flat lesions such as carcinoma in situ as a decisive impact on case outcome. Since the 1960s, many substances have been introduced to improve the detection of the cancerous tissue. In particular, photosensitizers of the bladder mucosa have been studied to achieve a chromatic contrast between normal and cancerous tissue. In 1994, Kriegmair et al. used intravesical instillation photosensitizing agent instead of the systemic administration route [15]. This is a precursor in the heme biosynthetic
pathway that induces intracellular accumulation of endogenous protoporphyrin IX (PpIX) if provided exogenously in excess [16]. A solution of hexaminolevulinate (HAL) and sodium hydrogen carbonate was instilled in the bladder 1,5-3,5 hours before planned TURB; it was prepared by dissolution of 1,5 g photosensitizing agent in 50 mL sodium hydrogen carbonate to a final pH of 4.8 to 5.0. The solution was freshly prepared immediately before instillation and filtered through a 0.2-µm filter for sterilization. The patients who were not able to hold their urine during the period requested received antispastic drugs to delay the urinary stimulus as much as possible. During cystoscopy an illumination system represented the source of light. This system alternatively emits white achromatic light and blue light (#=350-400 nm) [17].

CT equipment and scanning protocols

All examinations were performed on a 64-multidetector spiral CT Dual Source with the following parameters: 200 mAs (80 mAs in case of double acquisition-prone and supine position-according to emptying and bladder relaxation- figure 1-), 120 kV, effective slice thickness 0,6 mm, collimation 0.6 mm, reconstruction increment 0.4 mm, smooth kernel (B30), rotation speed 0.5 s, spatial resolution (X) 0.4 mm(Y) 0.4 mm (Z) 0.4 mm. Scans were obtained with patients in both the supine and prone position to prevent possible residual fluid obscuring small mural lesions. FOV was individualised in selected cases (for lesion over than 1 cm) to allow complete evaluation of the pelvis, with visualization of the bladder and extra-vescical structures (mean FOV 30-40cm) after administration of contrast agent i.v.

Fig.: Sagittal multiplanar reproduction (MPR) images used for scoring bladder distension: optimal distension coincided with the insufflation of 450-350 ml of air (a), whereas satisfactory (b) and poor (c) distension levels were usually obtained with 350-250 ml and

References: Department of Radiological Sciences, University of Rome - Rome/IT

Post-processing and image analysis
Data sets obtained were transferred in real time to a workstation (Syngo MMWP VE31A Win NT 5.2 Service Pack 2, COEM VE10D 64 Bit) for 3D processing and analysis. For each scan, we used multiplanar reconstructions (MPR) in the sagittal and coronal planes and volume rendering (VR) for endoluminal viewing (virtual endoscopy). Each examination was analysed in a double-blind fashion by two radiologists with 10 years of experience in virtual endoscopy and who were unaware of patients’ clinical data. Image analysis was performed over three reading sessions held approximately 1 week apart in which the order of the patients was changed each time. During the three reading sessions, the radiologists first assessed supine and prone sagittal images and then MPR and VR images. For each step, the radiologists expressed a diagnostic judgment on any lesion. Bladder lumen and mucosa were studied with a pulmonary window level setting (1,500/-700 HU); bladder walls and extraluminal structures were studied with an abdominal-level setting (400/40 HU). For virtual cystoscopy, we used the 3D lit fly-through with direct lightshiny rendering and CT fat-muscle-bone coloring (window level 1500/-200) supplied with the CT colonoscopy software. Additionally, we calculated the time required for reconstruction of each examination, considering both the CTC and VC techniques.
Results

The study population was divided into three groups according to the size of bladder lesions identified at PDD cystoscopy:

- Group 1: lesions with maximum diameter from 1 mm to 5 mm
- Group 2: lesions between 5.1 mm and 9 mm
- Group 3: lesions larger than 9.1 mm.

Statistical analysis was carried out by calculating sensitivity and specificity of the single techniques (CTC in supine and prone position; VC in supine and prone position; overall CT examination considering both positions) for each group. Furthermore, we conducted a detailed analysis of the first group using receiver operating characteristic (ROC) curves to determine, for each technique taken alone and in combination, the lowest size threshold at which the method showed the best level of diagnostic accuracy. In the same way, image results were compared with those of a PDDs cystoscopy performed after 1 week. AUC value of CT overall curve is comparable to AUC of conventional cystoscopy and lower than PDDs cystoscopy reflecting it's diagnostic superiority. In all statistical tests, a level of p<0.05 was considered significant (figure 2).
Fig.: Receiver operating characteristic (ROC) curves to determine for each technique taken alone and in combination the best level of diagnostic accuracy. AUC value of CT overall curve is comparable to AUC of cystoscopy.

**References:** Department of Radiological Sciences, University of Rome - Rome/IT

Cystoscopy

Cystoscopy visualised 92 lesions in the 44 subjects examined. Histopathology revealed the presence of neoplastic cells in 66 resected specimens, 56 of which were in pre-surgical patients and 10 in post-TURB patients (52 lesions were transitional-cell carcinoma, ten were clear-cell adenocarcinoma and four were small-cell carcinomas). Considering the subdivision of lesions into subgroups, 29 positive lesions were identified in 16 patients in group 1, with lesions <5 mm (ten pre-surgical and six post-TURB patients; size range 1.3-5 mm; mean 3.4 mm; median 3.5 mm; standard deviation (SD) 0.83), 20 positive lesions were identified in 14 patients in group 2, with lesions between 5.1 and 9 mm (nine pre-surgical and five post-TURB patients; size range 5.2-9 mm; mean 7.2 mm; median 7.35 mm; SD 1.196), and 17 positive lesions were identified in 14 patients in group 3, with lesions >9.1 mm (12 pre-surgical patients and two post-TURB patient; size range 9.3-22 mm; mean 12.42 mm; median 11 mm; SD 3.46) (Table 1).

<table>
<thead>
<tr>
<th>Patients selected</th>
<th>Lesions detected</th>
<th>Smallest</th>
<th>Largest</th>
<th>Arithmetic mean</th>
<th>95% CI</th>
<th>Median</th>
<th>95% CI</th>
<th>Variance</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>44 (30 pre-surgical/14 post-TURB)</td>
<td>92 (66 neoplastic/26 negative)</td>
<td>1.5 mm</td>
<td>5.0 mm</td>
<td>3.43 mm</td>
<td>3.1732–3.6935</td>
<td>3.5 mm</td>
<td>3.3000–3.8696</td>
<td>0.6969</td>
<td>0.8348</td>
</tr>
<tr>
<td>16 (10 pre-surgical/6 post-TURB)</td>
<td>29 neoplastic/13 negative</td>
<td>5.2 mm</td>
<td>9 mm</td>
<td>7.27 mm</td>
<td>6.6775–7.35 mm</td>
<td>7.5 mm</td>
<td>6.3382–8.2544</td>
<td>1.4304</td>
<td>1.196</td>
</tr>
<tr>
<td>14 (9 pre-surgical/5 post-TURB)</td>
<td>20 neoplastic/9 negative</td>
<td>9.3 mm</td>
<td>22 mm</td>
<td>12.42 mm</td>
<td>10.5096–11 mm</td>
<td>11 mm</td>
<td>9.8592–14.5904</td>
<td>11.9835</td>
<td>3.4617</td>
</tr>
<tr>
<td>14 (12 pre-surgical/2 post-TURB)</td>
<td>17 neoplastic/4 negative</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; TURB, transurethral resection of the bladder

Fig.: Results at Photodynamic diagnosis cystoscopy (PDDs) and classification of patients into subgroups, depending on lesion size.

**References:** Department of Radiological Sciences, University of Rome - Rome/IT

CTC and VC

The exam was good tolerated by patients, but remains the complications related to patient position, catheter removal or use of contrast material. Mean examination time, excluding catheter insertion, was 8±2 min. Reconstruction of raw data produced approximately 800 images for each data set (considering both supine and prone scans), with an additional 400 images in the case of contrast-enhanced imaging for staging purposes. Mean CTC/
VC reconstruction time was 10±3 min, with a mean reporting time of 15±2 min. Bladder distension was optimal in 30 cases, satisfactory in five and poor in three. Image quality was optimal in all cases for both CTC and VC.

Group 1 (lesions between 1 mm and 5 mm on page 15)

In 16 patients in group 1 (ten pre-surgical and six post-TURB), lesion size ranged from 1.4 mm to 5 mm (mean 3.8 mm; median 3.7 mm; SD 1.12. Statistical analysis of the results obtained with prone CTC alone revealed a sensitivity of 75.86%, a specificity of 84.62%, a positive predictive value (PPV) of 92% and a negative predictive value (NPV) of 61.11%, whereas supine CTC had 68.97% sensitivity, 76.92% specificity, 86.96% PPV and 52.63% NPV. Prone VC had a sensitivity of 89.66%, a specificity of 92.31%, a PPV of 96.30% and an NPV of 80%, whereas supine VC had 82.76% sensitivity, 92.31% specificity, 96% PPV and 70.59% NPV. Combined assessment of images obtained with the different techniques and positions (overall CT) revealed markedly higher values, with 93.10% sensitivity, 92.31% specificity, 96.43% PPV and 85.71% NPV (Table 2).

ROC curve analysis also showed that the combined approach substantially decreases the lower dimensional threshold at which maximum diagnostic accuracy is preserved (prone CTC 2.4 mm; supine CTC 2.1 mm; prone VC 1.9; supine VC 2 mm; overall CT 1.4 mm). A detailed account of the results of this analysis is given in Table 3 and Fig. 5.
Fig.: Statistical analysis of results achieved with the single and combined techniques in the different patient positions. It is interesting to note how diagnostic capability increases gradually as lesion size increases in groups 2 and 3. These data should, however, be regarded as indicative owing to the small size of the patient population enrolled in this preliminary experience.

**References:** Department of Radiological Sciences, University of Rome - Rome/IT

Likewise, ROC curve analysis revealed constantly higher area under-the-curve (AUC) values (greater diagnostic accuracy) for the combined approach compared with the single approach (prone CTC 0.844; supine CTC 0.809; prone VC 0.944; supine VC 0.901; overall CT 0.963) (Table 3).

Table 3

<table>
<thead>
<tr>
<th></th>
<th>CTC prone</th>
<th>CTC supine</th>
<th>VC prone</th>
<th>VC supine</th>
<th>CT overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC values</strong></td>
<td>0.844</td>
<td>0.809</td>
<td>0.944</td>
<td>0.901</td>
<td>0.963</td>
</tr>
<tr>
<td><strong>Lesion size</strong></td>
<td>&gt;2.4 mm</td>
<td>&gt;2.1 mm</td>
<td>&gt;1.9 mm</td>
<td>&gt;2 mm</td>
<td>&gt;1.4 mm</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>68.97%</td>
<td>68.97%</td>
<td>89.66%</td>
<td>82.76%</td>
<td>93.1%</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>49.2–84.7</td>
<td>49.2–84.7</td>
<td>72.6–97.7</td>
<td>64.2–94.1</td>
<td>77.2–99.0</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>92.31%</td>
<td>100%</td>
<td>75.1–100.0</td>
<td>75.1–100.0</td>
<td>75.1–100.0</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>65.9–98.7</td>
<td>75.1–100.0</td>
<td>75.1–100.0</td>
<td>75.1–100.0</td>
<td>75.1–100.0</td>
</tr>
</tbody>
</table>

Fig.: Results of receiver operating characteristic (ROC) curve analysis in group 1. The area under the curve (AUC), reflecting the accuracy of each diagnostic approach [computed tomography cystography (CTC) and virtual cystoscopy (VC) alone vs combined approach], demonstrates the constant superiority of the combined approach. The combined study is also associated with a decrease in the lower dimensional cutoff value and a linear rise in sensitivity and specificity.

**References:** Department of Radiological Sciences, University of Rome - Rome/IT

ROC curve analysis also showed that the combined approach substantially decreases the lower dimensional threshold at which maximum diagnostic accuracy is preserved (prone CTC 2.4 mm; supine CTC 2.1 mm; prone VC 1.9; supine VC 2 mm; overall CT 1.4 mm). A detailed account of the results of this analysis is given in Table 3.
**Fig.**: Receiver Operating Characteristic (ROC) plot curves illustrating the situation reported in Table 3. The area under the curve related to combined computed tomography cystography (CTC) and virtual cystoscopy (VC) (CT overall) is greater compared with those of CTC and VC alone, reflecting the superiority of the combined approach.

**References:** Department of Radiological Sciences, University of Rome - Rome/IT

Group 2 (lesions between 5.1 and 9 mm on page 15)

In the 14 patients in group 2 (9 pre-surgical and 5 post-TURB), lesion size ranged from 5.2 mm to 9 mm (mean 7.3 mm; median 7.3 mm; SD 1.19). Statistical analysis of the results of prone CTC alone revealed a sensitivity of 88.89%, a specificity of 88.89%, a PPV of 94.12% and an NPV of 80%, whereas supine CTC had 94.44% sensitivity, 88.89% specificity, 94.44% PPV and 88.89% NPV. Prone VC had a sensitivity of 100%, a specificity of 88.89%, a PPV of 94.74% and an NPV of 100%, whereas supine
VC had 100% sensitivity, 88.89% specificity, 94.74% PPV and 100% NPV. Combined assessment of the images obtained with the different techniques and positions (overall CT) showed, also in this group, markedly higher values, with 100% sensitivity, 100% specificity, 100% PPV and 100% NPV (Table 2).

Group 3 (lesions larger than 9 mm on page 16)

In the 14 patients in group 3 (12 pre-surgical and two post-TURB), lesion size ranged from 9.3 mm to 22 mm (figure 8) (mean 12.42 mm; median 11 mm; SD 3.46. Sensitivity and specificity in lesion detection was 100% for both CTC (prone and supine) and VC (prone and supine) (Table 2).

The two approaches (2D and 3D) are complementary, and in some cases, 3D images are absolutely necessary for the diagnosis. Evaluation of lesions <5 mm requires meticulous patient preparation, especially with regard to bladder distension; in fact, our analysis of interrater agreement seems in part to reflect the difficulties encountered by Song et al., showing a decreased ability to identify and measure lesions <5 mm. However, this finding applies to <30% of patients in group 1 and is, we believe, related to the degree of bladder distension, a crucial factor when evaluating very small lesions. In particular, in several cases with irregular appearance of the mucosal surface, bladder-wall evaluation was limited by poor bladder distension. However, air insufflation has been shown to be superior to positive opacification due to the higher attenuation gradients achievable with low tube current (#100 mAs) and fewer artefacts on virtual reconstructions [18]. Use of both techniques (2D and 3D) improves sensitivity in all patients with optimal or satisfactory bladder distension. Technical considerations include a short scanning time (3.5 s), which did not affect image quality with movement artefacts. The optimal attenuation gradient achieved between the air-dilated bladder lumen and the surrounding soft tissue allowed both tube current and radiation exposure to be significantly reduced in comparison with other studies [13, 14, 19]. The use of a new generation MDCT Dual Source combined with a high-resolution protocol with low values for slice thickness (1 mm), collimation (0.6 mm) and reconstruction increment (0.4 mm) enabled accurate, high resolution and fast exploration of the entire region of interest, offering reliable views for lesion detection. On the other hand, the high spatial resolution achieved with this thin-slice scanning protocol substantially increases the number of images and the amount of data acquired, requiring a dedicated workstation to efficiently handle data and reconstruct images. In contrast, CTC images were evaluated together with MPR reconstructions, as this allowed not only evaluation of axial images but also reliable multidimensional visualization (sagittal, coronal and oblique). Among the various 3D techniques available, we chose VC because it is relatively familiar to radiologists specialising in virtual endoscopy, is widely accepted by clinicians and surgeons owing to its similarity to actual endoscopy and, most importantly, because of the better image quality reported in previous reports [2, 20]. The contribution of the 3D approach on page was fundamental. Not only did it depict all lesions seen on 2D images, it also
served as a diagnostic modality for lesions in subjects with suboptimal bladder distension and in patients with irregular and hypertrophic mucosa. In some cases, CTC failed to discern between the folds of hypertrophic mucosa and bladder lesions, whereas VC allowed correct evaluation of the mucosal folds and a clear distinction between lesions and surrounding tissues. Moreover, VC allowed detailed inspection of the bladder neck, anterior wall and bladder diverticula, all sites that are recognised as potential blind spots at conventional cystoscopy [20].

Fig.: The contribution of the 3D approach was fundamental because it also served as a diagnostic modality for lesions in patients with irregular and hypertrophic mucosa. CTC axial (a) and sagittal (b) images failed to discern between the folds of hypertrophic mucosa and bladder lesions. VC allowed correct evaluation of the mucosal folds and a clear distinction between lesions (arrow) and surrounding tissues (c). High spatial resolution on the volume-rendering image (d) shows a polypoid lesion (arrow).

References: Department of Radiological Sciences, University of Rome - Rome/IT
Fig. 0: A small, 3-mm lesion located on the bladder dome. The high-resolution scan protocol, despite fluid residual and satisfactory bladder distension allowed clear depiction of the lesion on both sagittal (a) and axial images (b). On the volume-rendered image (c), the lesion appears as a regularly shaped polyp. Histopathological examination after resection during PDDs cystoscopy demonstrated the presence of neoplastic transitional cells.

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**Fig. 0:** A 6-mm, pedunculated lesion located on the left-posterior wall of the bladder in native axial contrast-enhanced CT image in supine (a) and sagittal multiplanar reproduction (MPR) images in prone position (c) and with bone-removal reconstruction. The high spatial resolution on the volume-rendered image (d), shows a polipoid lesion. Histopathological examination after resection during conventional (e) and PDDs cystoscopy demonstrated the presence of neoplastic transitional cells.

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Fig. 0: A large, 20-mm lesion on the anterior bladder wall (*) in sagittal (a) and axial (b) images. The high spatial resolution of the volume-rendered reconstructions allows excellent definition of the virtual cystoscopy (VC) images (c), which are closely comparable with those of conventional endoscopy (d).

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Conclusion

Our results suggest that CTC with VC represents a valuable and non invasive diagnostic method for detecting recurrent or de novo bladder cancers ranging from 2 mm to 9 mm in size. In particular, the analysis of results obtained in the group of lesions <5 mm demonstrated that the combined CTC and VC approach not only increases sensitivity and specificity in detecting suspicious lesions (93.10% sensitivity and 92.31% specificity) but, more importantly, decreases the lower dimensional threshold for lesion detection. CTC with Dual Source technique and VC are promising diagnostic approach both for new and recurrent locoregional bladders measuring in the range of 1-5mm. This technique is less invasive than conventional cystoscopy and can be used to evaluate areas difficult to assess with cystoscopy such as the anterior bladder neck. The main disadvantage of CTC and VC is the low sensitivity to depict flat lesions as demonstrate on cystoscopy with PDD method. In comparison with conventional cystoscopy, CTC and VC are less invasive and, in addition to depicting lesions directly, allow precise measurement of lesion size and evaluation of wall thickness. Furthermore, the 2D images permit evaluation of the locoregional extension of disease. Additional advantages are accurate depiction of the bladder lumen in all patients, including those with severe urethral stricture or hematuria. The main disadvantages of VC include the inability to perform endoscopic resections or biopsies and acquire in vivo information about the color and structure of the mucosa, as reported by others [21-23]; the latter limitation may affect detection rates in flat lesions[5], although we were unable to verify this owing to the lack of flat lesions in our series. A final disadvantage is exposure to ionising radiation. However, the advent of technologically advanced scanners has in part overcome this problem, as radiation doses can be reduced by using the dose-modulation software (Care Dose) supplied with the scanning equipment. CTC combined with VC can, however, be used in cases in which conventional cystoscopy is contraindicated or difficult to perform and in the follow-up of patients after surgery [24]. In such cases, should VC prove negative, the technique could spare the patient further conventional cystoscopy studies or provide the clinician and endoscopist with basic indications regarding bladder-wall morphology. Our study should, however, be considered a preliminary experience owing to the small number of patients examined. Further studies with state-of-the-art multidetector equipment need to be conducted on larger and more homogeneous patient populations to achieve higher statistical power.
References


