Investigation of Bladder Tumors with CT Urography in Patients Presenting with Gross Hematuria

MALIN HELENIUS
Bladder tumor is the most common tumor detected in patients presenting with gross hematuria. Early detection and treatment is crucial for good prognosis, however, delay in diagnosis and treatment is common. Routine work-up of gross hematuria includes cystoscopy and Computed Tomography Urography (CTU). If CTU has a high detection rate of bladder tumor, it can be used to direct further investigation of the patient, hopefully reducing delay to diagnosis and treatment. There is no consensus on which phase the bladder should be assessed at CTU. Assessment of the bladder in an early contrast-enhancing phase requires contrast material enhancement in bladder tumors and a bladder that is properly distended with urine. For patients younger than 50 years, the routine CTU protocol used for examining gross hematuria patients included unenhanced (UE), corticomedullary phase (CMP), and excretory phase (EP), with the start of the scan being enhancement triggered: patients aged 50 years or older followed the same protocol plus a nephrographic phase (NP).

The CTU protocol was compared with flexible cystoscopy for detecting bladder tumors. Sensitivity for bladder cancer detection was equal for CTU and cystoscopy (0.87).

Patients diagnosed with bladder cancer (n=50) were examined during UE, CMP, and EP, and 21 patients were additionally examined in NP. The highest mean tumor contrast enhancement was seen in CMP (37 HU).

The CMP, NP, and EP in 106 patients were randomized into an evaluation order (n=318 different phases) and blindly reviewed by two uroradiologists. In CMP, sensitivity (0.95) and negative predictive value (0.99) were higher than in NP and EP.

Four different preparation protocols for achieving bladder distension were compared. The protocol that included drinking 1 l of fluid during a two-hour period prior to examination without voiding during that period, gave satisfactory bladder distension without causing unacceptable patient discomfort and having the lowest compliance.

Gross hematuria patients should be primarily examined with CTU including UE, CMP and EP to direct further investigation of the patients. The patients should follow a preparation protocol including drinking 1 l of fluid during a two-hour period before examination and not voiding during that period.

Keywords: CT Urography, Bladder tumor, Gross hematuria, Tissue characterization, Bladder distension, Tumor detection

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"Har du bokat datum för disputation? Då måste du börja med det viktigaste; boka lokal för festen och bestämma framsidan på avhandlingen!"
Johan Wikström i fikarummet

"Nu är det ju inte så mycket mer att skriva."
Pär Dahlman när första artikeln var accepterad

To the boys that make my life important, Filip, Edvin and Torbjörn
Design, layout and illustrations:
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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Helenius M, Brekkan E, Dahlman P, Lönnemark M, Magnusson A.
   Bladder cancer detection in patients with gross hematuria: CT urography with enhancement triggered scan versus flexible cystoscopy.
   (Submitted)

II. Helenius M, Dahlman P, Magnusson M, Lönnemark M, Magnusson A.
   Contrast enhancement in bladder tumors examined with CT urography using traditional scan phases.

III. Helenius M, Dahlman P, Lönnemark M, Brekkan E, Wernroth L, Magnusson A.
    Comparison of the traditional post contrast CT Urography phases in bladder cancer detection.
    (Submitted)

IV. Helenius M, Segelsjö M, Dahlman P, Magnusson A.
    Comparison of four different preparation protocols to achieve bladder distension in patients with gross haematuria undergoing a CT Urography.

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# Abbreviations

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>CMP</td>
<td>Corticomedullary phase</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CTU</td>
<td>Computed Tomography Urography</td>
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<td>CIS</td>
<td>Carcinoma <em>in situ</em></td>
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<td>EP</td>
<td>Excretory phase</td>
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<tr>
<td>HU</td>
<td>Hounsfield units</td>
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<tr>
<td>kV</td>
<td>Kilovolts</td>
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<tr>
<td>mAs</td>
<td>Milliamperes-seconds</td>
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<tr>
<td>MDCT</td>
<td>Multi detector computed tomography</td>
</tr>
<tr>
<td>NP</td>
<td>Nephrographic phase</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>RCC</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma <em>in situ</em></td>
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<tr>
<td>TNM</td>
<td>Tumor Node Metastasis</td>
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<tr>
<td>TUR-B</td>
<td>Transurethral resection of the bladder</td>
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<tr>
<td>UCC</td>
<td>Urothelial cell carcinoma</td>
</tr>
<tr>
<td>UE</td>
<td>Unenhanced phase</td>
</tr>
<tr>
<td>UP</td>
<td>Urothelial phase</td>
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</table>
Introduction

Hematuria

Hematuria, meaning blood in the urine, can be either microscopic or macroscopic (gross). In microscopic hematuria, the blood in the urine is not visible and has to be detected by urine dipstick analysis. In Sweden, recommendations are that microscopic hematuria should not be further investigated, as the correlation with underlying disease is low (1, 2). When the blood in the urine is visible, it is called gross hematuria, or macroscopic hematuria. In 1 liter urine, 1 ml blood colors the urine red and the concentration of red blood cells then equals or exceeds $5 \times 10^9/l$ (3).

However, blood is not the only reason that urine can be red, pigmenturia can be due to (4):

1. Consumption of beetroot and in some cases, carrots.
2. Consumption of medicines such as doxorubicin and nitrofurantoin.
3. Porphyria, a genetic disorder with a deficiency of an enzyme participating in the porphyrin and heme biosynthesis, characterized by attacks during which the urine can be red.
4. Paroxysmal nocturnal hemoglobinuria (PNH), a disease characterized by intravascular hemolytic anemia (destruction of red blood cells in the blood vessels) causing excretion of hemoglobin (the material inside the red blood cells that transports oxygen and is red) into the urine.
5. Hemo-/myoglobinuria caused by for example toxins or chemicals, autoimmune hemolysis (the immune system attacks and destroys red blood cells inside the blood vessels), mechanical impact due to repetitive trauma to the body during excessive exercising, and muscle necrosis.

Urine dipstick analysis is positive only for PNH and hemo-/myoglobinuria and can be used to distinguish the consumption of beetroot and medicines and porphyria from hematuria.

Gross hematuria can be combined with other symptoms from the urinary tract, such as pain or urgency, or be silent when there are no associated symptoms.

Although the prevalence of gross hematuria in an unselected population has not been fully analyzed, in a population-based study from western Sweden, 247 patients were referred to a Urology clinic due to gross hematuria during one year, which corresponded to an incidence of 100/100,000 per year (5).
Gross hematuria is approximately three times more common in men than in women (5, 6).

Gross hematuria is not only a diagnosis. It is a symptom with an underlying cause, which is often serious and 15–28% of patients with gross hematuria have a malignancy in the urinary tract as the underlying cause (5-9).

When examining patients with gross hematuria, the most common tumor found in up to 20% of patients, is bladder cancer (5, 7). Other tumors causing gross hematuria are renal cancer, urothelial cell carcinoma (UCC) of the renal pelvis and the ureters, and prostate cancer.

Nonmalignant causes of gross hematuria are urinary tract infection, stones in the kidneys, ureters, or the bladder, benign prostate hyperplasia, anticoagulant treatment (Warfarin) and IgA nephritis (10). Urinary tract infection is the most common nonmalignant cause reported, and as with kidney stones, is often associated with other symptoms such as fever, urgency, and pain.

Patients with gross hematuria must be asked about:

1. Intake of medicines or food that can cause the urine to be red
2. Symptom debut after trauma and/or excessive physical activity
3. Anticoagulant treatment (Warfarin)

In cases with obvious cause to the gross hematuria (e.g. hemorrhagic cystitis in a woman, Warfarin treatment with high INR or bladder catheter), investigation initiation is not necessary. In all other cases, gross hematuria investigation must be initiated. As the risk of a malignancy being the underlying cause of the gross hematuria is substantial, the investigation should be finished within 4 weeks (4).

**Bladder cancer**

Bladder cancer is the sixth most common tumor form in Sweden and represents approximately 4.5% of all new tumor cases. In 2006, 2300 new cases of bladder cancer were registered (1701 men and 599 women) and 644 patients died from bladder cancer the same year (466 men and 178 women). Since 1960, the incidence of bladder cancer has more than tripled in Sweden and the risk of developing bladder cancer increases with age, mean age at diagnosis is 73 years. The population is older than in 1960 and consequently, the incidence of bladder cancer has increased (11).
Approximately 70% of patients with bladder cancer present with gross hematuria (12) and up to 20% of patients with gross hematuria are diagnosed with bladder cancer (5, 7). Other symptoms of bladder cancer can be pain when urinating or irritative symptoms in the bladder region, especially when carcinoma \textit{in situ} is the case.

Cigarette smoking increases the risk of developing bladder cancer by 2–5 times (13). The second most important risk factor is occupational chemical exposure in industries dealing with for example dyes, paints, textiles, and leathers. Other examples of risk factors for developing bladder cancer are ionizing radiation (e.g. radiotherapy in gynecological malignancies), arsenic, and cyclofosfamid (chemotherapy) (14). No hereditary bladder cancer form is known.

More than 90% of bladder tumors are UCC, a few percent are squamous cell carcinomas, and approximately one percent is adenocarcinoma.

The TNM (Tumor, Node, Metastasis) classification approved by the UICC (Union International Contre le Cancer) describes the tumor distribution (15, 16) (Table 1, Figure 1). The description includes whether the tumor is locally invasive or not (how deep into the bladder wall it is growing), whether the tumor has spread to lymph nodes or not, and whether other organs are affected or not.

Tumor differentiation means how much the tumor cells resemble the normal bladder cells. If tumor differentiation is low, the resemblance is low, and if the differentiation is high, the resemblance is high.

Tumor differentiation in non-muscle-invasive tumors is described by a grading system developed by WHO and the International Society of Urological Pathology (ISUP) (17, 18) (Table 2). Most clinical studies have used a previous version of the grading system from 1973. A newer version of the grading system from 2004 has not been fully evaluated. Until the 2004 grading system has been fully evaluated, both grading systems should be used when describing the tumors. The 2004 grading system contains a detailed histological description of the various grades and has better reproducibility than the previous system from 1973. All muscle-invasive tumors are high-grade urothelial carcinomas and no more prognostic information can be provided by grading muscle-invasive tumors (19).

Both TNM classification and WHO grading system, if applicable, should be used when reporting the tumor, as this is a prognostic factor and decides the treatment.
Table 1.
TNM classification.

<table>
<thead>
<tr>
<th>T - Primary tumor</th>
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<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis Carcinoma <em>in situ</em> ‘flat tumor’</td>
</tr>
<tr>
<td>T1 Tumor invades subepithelial connective tissue</td>
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<tr>
<td>T2 Tumor invades muscle</td>
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<tr>
<td>T2a Tumor invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b Tumor invades deep muscle (outer half)</td>
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<tr>
<td>T3 Tumor invades perivesical tissue:</td>
</tr>
<tr>
<td>T3a Microscopically</td>
</tr>
<tr>
<td>T3b Macroscopically (extravesical mass)</td>
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<td>T4 Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a Tumor invades prostate, uterus or vagina</td>
</tr>
<tr>
<td>T4b Tumor invades pelvic wall or abdominal wall</td>
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<table>
<thead>
<tr>
<th>N - Lymph nodes</th>
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<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
</tr>
<tr>
<td>N2 Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)</td>
</tr>
<tr>
<td>N3 Metastasis in common iliac lymph node(s)</td>
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<table>
<thead>
<tr>
<th>M - Distant metastasis</th>
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<tbody>
<tr>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>M1 Distant metastasis</td>
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</tbody>
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Table 2.
WHO grading system.

<table>
<thead>
<tr>
<th>1973 WHO grading</th>
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<tr>
<td>Urothelial papilloma</td>
</tr>
<tr>
<td>Grade 1: well differentiated</td>
</tr>
<tr>
<td>Grade 2: moderately differentiated</td>
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<tr>
<td>Grade 3: poorly differentiated</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2004 WHO grading</th>
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<tbody>
<tr>
<td>Flat lesions (urothelial hyperplasia, reactive urothelial atypia, atypia of unknown significance, dysplasia and carcinoma <em>in situ</em>)</td>
</tr>
<tr>
<td>Urothelial papilloma</td>
</tr>
<tr>
<td>Papillary urothelial neoplasm of low malignant potential (PUNLMP)</td>
</tr>
<tr>
<td>Low-grade papillary urothelial carcinoma</td>
</tr>
<tr>
<td>High-grade papillary urothelial carcinoma</td>
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</table>
Carcinoma in situ (Tis or CIS) is a low differentiated tumor (grade 3), and not a cancer precursor, that is flat and can be missed at cystoscopy, if it is not biopsied. There are often multi-focal lesions that can exist in the upper urinary tract, prostatic ducts and urethra.

There are three types of CIS:
1. Primary: isolated CIS with no previous or concurrent exophytic tumors
2. Secondary: CIS detected during the follow-up of patients with a previous tumor
3. Concurrent: CIS in the presence of exophytic tumors

Approximately 54% of patients with CIS will develop muscle-invasive disease if not treated (20), and there is no prognostic factor to predict the outcome.
Bladder cancer is a heterogeneous disease with great variation in malignancy grade, tendency to multi-focal appearance, and relapse. Fast investigation is crucial for good prognosis. The 3-year survival rate for bladder cancer is reduced from 60% to 25%, if the treatment is delayed more than 4 weeks after the gross hematuria debut (21) and 5-year survival is decreased when contact with an urology clinic is delayed more than 14 days after the gross hematuria debut (22). However, delay in diagnosis and treatment is common (23-25).

Approximately 70% of bladder tumors are non-muscle-invasive (Ta, T1 or CIS) when diagnosed: 30% of bladder tumors are muscle invasive and less than 50% of these patients survive 5 years (26). Bladder cancer tends to metastasize, mainly to local lymph nodes but also to liver, lungs, and bone. Many muscle invasive tumors are suspected to already have metastasized microscopically before diagnosis (27).

**Hematuria investigation**

Excretory urography used to be the primary imaging method in patients with gross hematuria. However, excretory urography has low sensitivity for detecting bladder cancer and all patients have to undergo cystoscopy to evaluate the bladder. Computed tomography urography (CTU) has replaced excretory urography, but all patients are still routinely examined by cystoscopy. Recommended primary diagnostic tools for patients presenting with gross hematuria are CTU and flexible cystoscopy, including cytology (28). The computed tomography (CT) technique has evolved rapidly since the 20th century and modern multi-detector row CT scanners allow fast scanning of the entire abdomen in a few seconds and generate high-resolution images that can be reconstructed in multiple planes, which sharpen and optimize diagnostics.

**Flexible cystoscopy**

Flexible cystoscopy is performed by an urologist. The bladder is dilated with saline solution to make it easier to examine. The entire bladder and urethra are examined and pathological findings can be biopsied. Location, size, number and appearance (flat or exophytic) of any findings are described (15).

CIS can present as reddish areas that are difficult to distinguish from inflammation (29). Sometimes CIS is not visible, and if CIS is suspected mapping biopsies are performed from presumably normal tissue in several predefined locations in the bladder and resection from the prostatic part of the bladder in men and the bladder neck in women.
Cytology from the fluid used during cystoscopy is analyzed (28) and with positive cytology and normal cystoscopy, mapping biopsies are performed (11). Photodynamic examination with blue light after installation of the fluorescence substance, Hexaminolevulinat, can increase the possibility of discovering bladder cancer, especially CIS and flat tumors (30-33), and help guide biopsies (29).

**TUR-B**

When a bladder tumor diagnosis is established, endoscopic resection of as much of the tumor as possible is performed; transurethral resection of the bladder (TUR-B). The goal with TUR-B is to make the correct diagnosis and remove all visible tumor parts. Tumors that are <1 cm in size can be resected in one piece, including the tumor and underlying bladder wall. With larger tumors, the resection should be in fractions, meaning that superficial and profound parts of the tumor are separated and can be analyzed separately. If multiple tumors are present, the tumor resections should be separated to enable separate analyzes of the tumors. Bladder muscle must be included in the material resected to enable evaluation of possible muscle invasion (15).

The resected tumor is analyzed by pathologists and used to report bladder tumor classification (“T” in TNM classification) and grading (tumor differentiation).

**Palpation**

When a bladder tumor is detected, bimanual palpation of the empty bladder is performed before and after TUR-B during muscle relaxing general anesthetics (28). The size of the palpable tumor is reported, and whether it is soft or firm, and mobile or fixed to the surrounding tissue. Before TUR-B, the examination provides prognostic information and guidance for evaluating tumor invasion. The examination after TUR-B is baseline for evaluating treatment effect (11).

**CTU**

CTU is defined as a CT examination of the urinary tract before and after administration of intravenous iodine contrast material, including a scan in excretory phase (EP) (34). However, there is no consensus about which phases should be included in a CTU. The concentration and amount of contrast material, injection rate, scan time delay, and phases used can vary and different combinations of these parameters results in different characteristics of the CTU protocol. For example, a small amount of contrast material with high concentration injected at a high rate results
in a short, but intense enhancement peak, whereas, a larger amount of contrast material with lower concentration injected at a lower rate results in a long enhancement peak with lower intensity (35).

The unenhanced phase (UE) is used to detect calculi and serve as a baseline attenuation value for calculating enhancement in masses and other abnormalities (Figure 2) (36).

![Figure 2.](image)
The most common phases in CTU; UE (A), CMP (B), NP (C) and EP (D).

In a contrast material enhanced phase, the renal parenchyma and vessels are evaluated. This phase is used to detect masses, traditionally renal masses, but urothelial tumors can be detected with this phase too. The traditional contrast material enhanced phases are corticomedullary phase (CMP), typically 25–35 s after the contrast material injections begins, and nephrographic phase (NP) usually 90–110 s after contrast material injection (34). The maximum contrast enhancement difference between the cortex and medulla in the kidneys is seen in CMP, whereas, the contrast enhancement is more homogeneous in the renal parenchyma in the NP (Figure 2). CTU protocols included both phases, but awareness of the high radiation doses this causes, lead to efforts to reduce the dose. A common way of reducing radiation dosage is to exclude the CMP, based on studies from the 1990s (37-41) that indicate a higher detection rate of small (<3 cm) renal masses in NP than in CMP (42). The most common lesions missed in CMP are medullary cysts, which have no clinical impact (42). However, CMP is the best phase for tumor staging, evaluation of vessel anatomy and possible tumor extension in the renal vein, pre-operative planning, and metastasis evaluation (43-45).

In the excretory phase (EP), usually performed with a delay of 300–960 s (34), the contrast material is excreted to the collecting system (calyces and renal pelvis), ureters, and bladder (Fig. 2). The EP is used for evaluating renal function, ureter anatomy, the relation between any renal
neoplasms and the collecting system (36), and for detecting tumors in the collecting system, ureters, and bladder (34, 46). In EP, the tumors present as filling defects (Figure 3).

![Image](image.png)

Figure 3.
Bladder assessment in EP. Tumors present as filling defects (arrow).

To obtain a homogeneous contrast material concentration in the bladder the patients might have to exercise between the contrast material enhanced phase and the excretory phase, e.g. be asked to touch their toes, walk around in the examination room, or turn around on the examination table multiple times (47, 48). Otherwise, the contrast material excreted to the bladder can be layered with the opacified urine on the bottom and the non-opacified urine on top (Figure 4). Bladder tumors in the anterior wall of the bladder can then be missed, as no contrast defects can be shown where there is no contrast.

The contrast concentration in the bladder must be sufficiently high to make the bladder tumors appear as contrast defects (Figure 5) and the bladder must be well distended for properly assessment. A common problem described when evaluating the bladder in EP is the inability to differentiate a thickening of the bladder wall from an incomplete filling of the bladder with contrast medium (48).

The EP may need to be performed with greater delay to achieve a well-distended bladder with urine homogeneously mixed with contrast material of adequate concentration. Consequently, examination times can increase. The EP may need to be performed several times and sometimes with the patient in different position (prone), if confident evaluation of the bladder cannot be done, resulting in increased radiation dose.
Figure 4.
Layering of the excreted contrast material in the bladder with the opacified urine on the bottom and the non-enhanced urine on top.

Figure 5.
Low contrast material concentration in the bladder; the attenuation in the tumor (arrow) and the contrast material blended urine is equal and the tumor cannot be detected (A). In the contrast material enhanced phase, the tumor is visualized as a contrast material enhancing mass (B).
An early contrast-enhancing phase, urothelial phase (UP) or portal venous phase, performed with a 60 or 70 s delay after the start of contrast material injection, has been used for bladder cancer detection with promising results (49-51). The bladder tumors then present as contrast material enhancing masses against the non-opacified urine in the bladder (Figure 6). The bladder must be sufficiently distended with urine for assessment in contrast-enhanced phase; this can be achieved by oral hydration, intravenous infusion of saline or intravenous administration of diuretics, or a combination of these.

Figure 6.
Bladder assessment in contrast enhancing phase. Tumors (arrow) present as contrast enhancing masses.

The advantage for the patients when evaluating the bladder in contrast enhanced phase instead of EP would be shorter examination times and less complicated procedures.

A fixed delay for the contrast-enhancing phase has been used which means that scanning can occur before or after the enhancement peak, depending on the patient’s cardiovascular function (49, 51, 52).

The UE covers the entire abdomen; the contrast material enhanced phase covers the kidneys or the entire abdomen, and the EP the entire abdomen.

To reduce radiation dose, combined phases, “split-bolus” protocols, can be used (34, 53), in which a first contrast material dose is given after UE, with a second dose being given after 2–15 minutes. A combined contrast material enhanced and EP phase is then obtained, usually combined NP and EP. The split-bolus phase can be generated by a smaller first injection of 30–50 mL of contrast material at a rate of 2 mL/s, followed by a larger
second injection of 80–100 mL at a rate of 2–2.5 mL/s after 2–15 min. Alternatively, a larger first injection of 75–100 mL of contrast material at a rate of 2–3 mL/s, followed by a smaller injection of 45–50 mL at a rate of 2–3 mL/s after 3–10 min can be used. Scan time is usually 90–120 s after the start of the second injection.

A combined CMP, NP, and EP protocol has been described (54). This “triple-bolus” protocol consists of a first injection of 30 mL of contrast material at a rate of 2 mL/s, followed by a second injection of 50 mL at a rate of 1.5 mL/s after 420 s, and a third injection of 65 mL at a rate of 3 mL/s 20 s after the second injection.

The amount of contrast material used is often 100–160 mL at a concentration of 300–370 mg I/mL with injection rates varying from 2 mL/s to 4 mL/s (34). Radiation doses vary between 10 and 35 mSv for CTU examinations (55, 56).

In addition to bladder cancer detection, CTU is used to investigate whether the tumor has spread to lymph nodes or metastasized to other organs. A CT of the thorax is performed to exclude lung metastasis in patients diagnosed with muscle invasive bladder cancer, “N” and “M” in TNM classification (28).

**CTU in Uppsala**

At Uppsala University Hospital, the routine CTU protocol for examining patients presenting with gross hematuria includes UE, CMP, NP, and EP for patients aged 50 years or older. To reduce radiation doses, the UE, NP and EP are performed with lower dose while the CMP is performed with normal dose. In patients younger than 50 years, the CTU protocol includes UE, CMP, and EP to reduce radiation doses further. The radiation dose in this protocol is approximately 10 mSv with the three-phase protocol and 13 mSv with the four-phase protocol.

CMP starts automatically with a 5 s delay when the attenuation in a region of interest (ROI) placed in the aorta at the level of the diaphragm reaches 200 HU, after administration of 60–80 ml of intravenous contrast material at a concentration of 350 mg I/ml and injection rate of 4 mL/s. The times for the contrast bolus to arrive in the aorta increases as cardiac output decreases (57), and the bolus tracking technique is used to individualize scan delays to improve contrast enhancement in the kidneys during CTU phases (58). Depending on the patients’ cardiovascular function, the CMP starts with a 25–45 s delay after the start of contrast
material injection. NP starts with a 40 s delay and EP starts with a 300 s delay after CMP is completed. The scan time of the CMP is approximately 10–15 s, resulting in a delay of 75–100 s for NP and 335–360 s for EP after the start of contrast material injection. All phases cover the entire abdomen.

The decision to use CMP instead of NP in all patients presenting with gross hematuria was based on the findings that renal tumors are usually >4 cm (59) when presenting with gross hematuria and small renal tumors (3 cm or smaller) are usually detected incidentally when the patient undergoes another radiological examination of the abdomen (60-62). Furthermore, the CMP is the best phase for renal tumor staging, pre-operative planning, and metastasis evaluation as metastases are often hypervascular (43-45, 63). In addition, the exclusion of NP does not reduce the ability to detect renal tumors (36). Bladder tumor is the most common tumor detected when examining patients presenting with gross hematuria (5, 7) and these tumors can present with gross hematuria even when they are still small. Consequently, a CTU protocol for examining patients with gross hematuria does not have to be designed for detecting small renal lesions, but for detecting urothelial tumors.

The experience at Uppsala University Hospital is that many bladder tumors are detected with CTU and some tumors detected with CTU are missed at cystoscopy. However, the detection rate of bladder cancer with an individually adjusted CTU protocol, compared to flexible cystoscopy, has not been evaluated.

Bladder tumors contrast-enhance in early phases with fixed time delay (52). However, in which phase the maximum contrast enhancement occurs and how high the contrast enhancement is when the scan is enhancement triggered and individually adjusted to the patients’ cardiovascular function, is unknown.

Similarly, it is not known which of the post contrast phases in our CTU protocol is best for bladder cancer detection. If CMP is proven to be equal, or possibly better than NP in detecting bladder tumors, then NP can be excluded from the CTU protocol.

Preparation protocols with instructions regarding fluid intake and voiding restrictions are used to obtain bladder distension as contrast enhancement phases are relied on for bladder assessment. Although different preparation protocols have been used in our institution, none has been properly evaluated.
Bladder cancer treatment

TUR-B
In Ta and T1 tumors, TUR-B is both a diagnostic tool and a treatment. Thus, it is crucial the initial resection is correct and complete (64). When the tumor is large and/or multi-focal, the risk of incomplete resection increases, and a second resection within 8 weeks after the initial treatment is recommended (28). Initially, T1 tumors tend to be under-staged, and at second resection up to 25% are muscle invasive (65, 66). A second resection is also recommended when a T1 or high-grade tumor is found (67) or when no muscle tissue is included in the initial resected material (64). Second resection increases recurrence-free survival (68).

Intravesical installations
Intravesical installations are solutions with antitumor effect given via a urinary catheter, and should be kept in the bladder for about 2 hours (28).

Bacillus Calmette-Guérin (BCG) is a live attenuated form of Mycobacterium bovis (the bacterium causing tuberculosis in cattle) and related to Mycobacterium tuberculosis (the bacterium causing tuberculosis in humans). The exact antitumor mechanism of BCG installations is unknown, but is considered an immunotherapy as it causes a local immune response.

Intravesical BCG installations are the first choice treatment for CIS. Intravesical chemotherapy installations (e.g. Mitomycin C) are second choice treatment, and can be used if BCG cannot be used (e.g. due to allergy or immunodepression). If the tumor remains after 6 months of treatment with installations, or if the tumor progresses during the installation treatment, cystectomy is recommended (28).

In non-muscle-invasive tumors, one dose of intravesical chemotherapy can be given to all patients with papillary tumors immediately after TUR-B (69). Additional installations of BCG or chemotherapy can be considered for frequently recurring tumors, tumors located in diverticula, and for all TaG3 and T1G1-3 tumors (28).

However, catheterization must be non-traumatic. The chemotherapy solution is highly corrosive to the skin and BCG installation can cause systemic side effects, such as pneumonia, hepatitis, and sepsis, if the bladder mucus membrane is injured during catheterization (28).
Cystectomy
Radical cystectomy is the gold standard treatment in patients with muscle invasive bladder cancer (T2-T4a, N0-Nx, M0). Non-muscle invasive tumors T1G3, recurrent superficial tumors, BCG resistant CIS, and extensive non-muscle invasive tumor that cannot be controlled with TUR-B and intravesical installations can also be indication for cystectomy (15).

In men, surgery includes extirpation of the bladder, prostate, seminal vesicles, and sometimes urethra. In women, the bladder and sometimes uterus, ovaries, and urethra are removed. Extirpation of regional lymph nodes is always included in the procedure for classifying the tumor (11).

In patients where the urethra has been preserved, an artificial bladder made of bowels, orthotopic neobladder, can be connected to the urethra to enable natural urination. When the urethra has been removed, a continent cutaneous urinary diversion can be made, an artificial bladder that can be emptied by self-catheterization through the abdominal wall. Bricker diversion (urostomy consisting of a detached part of ileum where the ureters are connected) is the simplest technique and used for patients that cannot tolerate more advanced surgery, such as elderly patients (11, 15).

Chemotherapy
Bladder cancer has moderate sensitivity to chemotherapy. Chemotherapy is administered as neoadjuvant treatment (before curative aiming cystectomy) which increases 5 year survival 5% compared with surgery alone (70), or as a therapy in metastatic disease where median survival can increase by 10 months compared to untreated disease (15, 71). There is no evidence adjuvant chemotherapy (additional chemotherapy after cystectomy) increases survival rate and it is not recommended (28, 72).

Radiotherapy
Radiotherapy can be given to patients who cannot undergo surgery and can be curative treatment (28).

In patients with inoperable locally invasive tumors (T4b), radiotherapy can be used as palliation (symptom relieving treatment) if complications, such as massive hematuria requiring blood transfusion, occur and is also effective as pain relief treatment in bone metastases (15, 28).
Aim of the thesis

General aim
The general aim of this thesis was to evaluate and improve the CTU protocol for bladder assessment in patients presenting with gross hematuria.

Specific aims

Paper I
To compare a CTU protocol, where the scan was enhancement triggered, with flexible cystoscopy for detecting bladder tumors in the same material.

Paper II
To study the attenuation and contrast material enhancement pattern in bladder tumors with a CTU protocol including UE, CMP, NP, and EP, where the scan was enhancement triggered.

Paper III
To investigate which post-contrast phase CMP, NP, or EP in a CTU protocol, where the start of the scan was enhancement triggered, was most suitable for bladder tumor detection.

Paper IV
To establish a preparation protocol for sufficient bladder distension that allowed confident evaluation of the bladder without causing unacceptable discomfort to the patient.
Materials and methods

Patients

During a three-year period (Oct 2005–Nov 2008) 563 adult patients (419 men and 144 women, with a mean age of 62±17 years: range 18–97 years) were referred for a CTU due to gross hematuria.

Medical records and histopathological data were reviewed to identify final diagnoses and cystoscopy results. In the medical records, 83 patients (15%) were diagnosed with bladder cancer.

The patients were prospectively recruited at the time of the CTU examination and the study was approved by the regional ethical review board in Uppsala. Informed consent was signed by all patients who could withdraw from the study at any time.

Paper I

Of the 563 patients, 128 were excluded. Exclusion criteria were: not being able to evaluate the bladder (e.g., undistended due to a catheter in the bladder or artifacts from hip prosthesis) (n=39), the bladder was only examined in UE (n=3), a history of previously treated bladder cancer (n=11), surgical removal of the bladder for reasons other than cancer (n=1), having undergone TUR-B or biopsy prior to CT (n=21), and unknown cystoscopy results (n=53). Thus, 435 patients (321 men and 114 women, with a mean age of 63±16 years: range 18–97 years) were included in the study.

Paper II

Of the 83 patients diagnosed with bladder cancer, 33 were excluded from the study. These were patients with a previous history of treated bladder cancer (n=6), patients who underwent TUR-B or a biopsy before CTU (n=17), patients whose bladders could not be evaluated due to lack of distension (e.g. catheter in the bladder) or beam hardening artifacts from hip prosthesis in the pelvis (n=6), patients with the bladder not examined in UE (n=1) and patients with tumors not detected during CTU (n=3). Thus, 50 patients were included in the study (37 men and 13 women, with a mean age of 70±14 years: range 22–93 years).
Paper III
Patients (n=111) undergoing the four phase CTU protocol were identified and 5 patients who had undergone TUR-B or biopsy before CTU were excluded. Thus, 106 patients (86 men and 20 women, with a mean age of 68±9 years: range 50–93 years) were included in the study: 21 patients (20%) were diagnosed with bladder tumor.

Paper IV
Of the 563 patients referred for CTU due to gross hematuria, 100 patients were randomly divided into four groups of 25 patients in each group, Table 3.

Table 3.
Mean age ± standard deviation (range), and gender distribution, in each group.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Age</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62±14 (range 23–82)</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>58±18 (range 18–83)</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>68±7 (range 55–81)</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>59±17 (range 25–86)</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>
Methods

CTU parameters

The CTU examinations were performed on two different CT scanners, Somatom Sensation 16 or Somatom Definition (Siemens Medical Solutions, Forchheim, Germany). The entire urinary tract was examined in all scan phases used.

Depending on body size, a dose of 60–80 ml of contrast material, iohexol, 350 mg I/ml (Omnipaque, GE Healthcare AS, Oslo, Norway) was administered at a rate of 4 ml/s with a power injector (Stellant D, Medrad Inc, Indianola, PA, USA). Immediately after the injection of contrast material, 40 ml of physiological saline was administered at the same injection rate. The CMP started automatically with a 5 s delay when the attenuation value in a region of interest (ROI), placed in the aorta at the level of the diaphragm, reached 200 Hounsfield units (HU). This corresponded to a delay of 25–45 s after the start of contrast material injection, depending on the patients’ cardiovascular function. After the CMP was completed, NP was performed with a 40 s delay and EP with a 300 s delay. The scan time of the CMP was approximately 15 s with Somatom Sensation 16 and 10 s with Somatom Definition, which meant NP had a delay of 75–100 s and EP had a delay of 335–360 s after the start of contrast material injection.

Tube voltage was 120 kV and the quality reference mAs was 60 for UE, 120 for CMP, and 80 for both NP and EP. The rotation time was 0.5 s, collimation was 16x0.75 mm (Sensation 16) and 64x0.6 mm (Definition), and pitch 1.0 mm (Sensation 16) and 0.9 mm (Definition). Automatic tube current modulation (CARE Dose 4D, Siemens Medical Solutions, Forchheim, Germany) was used and the effective tube current time setting was the input parameter for the Care Dose 4D software: consequently, the actual dose deviated slightly. Image reconstruction was performed with slice thickness of 3 mm with 2.5 mm increment in the axial plane and a slice thickness of 5 mm with 5 mm increment in the coronal plane.

Paper I

Different preparation protocols for achieving bladder distension were used, as patients in this study were also included in the study comparing different preparation protocols (Paper IV). Patients were asked to drink 500 or 1000 ml of fluid and not to void one or two hours before the examination.
The original CTU examination reports from the uroradiologists were retrospectively studied at a time point separately from the journal reviews and the results compared at the time for data analysis.

In patients diagnosed with bladder tumor, the CTU examinations were reanalyzed to determine whether tumors not mentioned in the initial report could be detected retrospectively, and to measure the size of the tumor in the axial plane (Figure 7). Any retrospectively detected tumors were not included in the calculations. The shortest tumor diameter was considered the most relevant measurement as this part of the tumor usually protrudes into the bladder, and bladder tumors can grow flat. As this diameter should contribute the most to tumor detection during CTU, this measurement was used in the study.

Figure 7.
Size measurement in CMP in axial plane.

In patients without bladder tumor diagnosis but with a CTU report describing a tumor (false positive findings), the CTU examination was also reanalyzed. The patients not diagnosed with bladder cancer when first presenting with gross hematuria had a follow-up of five to eight years through screening a cancer register (Regional Cancer Centre; RCC) to determine whether any tumors had been missed by both CTU and cystoscopy at the initial gross hematuria episode.

**Statistical analysis**
Data are expressed in absolute numbers and median values with (range).

Sensitivity, specificity, and positive and negative predictive values were calculated with standard statistical methods.
Paper II

All patients underwent CTU including UE, CMP, and EP. The four phase protocol including UE, CMP, NP, and EP was used to examine 21 patients. As patients in this study were also included in the comparison of different preparation protocols for bladder distension (Paper IV), different preparation protocols were used. The patients were asked to drink 500 or 1000 ml of fluid and not to void for one or two hours before the examination.

Attenuation measurements were made on the axial images with a circular ROI that was equally placed in the tumor in all phases (Figure 8). If the tumor was not visible in a phase, the ROI was placed in the tumor guided by the other phases where the tumor was visible. The ROI was made as big as possible in the center of the tumor to avoid false attenuation values from the urine. As placement of the ROI in central vessels in the tumor would result in falsely high attenuation values, this was also avoided.

![Attenuation measurement in HU on axial reconstructions in all phases; UE (41 HU), CMP (82 HU), NP (65 HU) and EP (57 HU).](image)

**Figure 8.**

Attenuation measurement in HU on axial reconstructions in all phases; UE (41 HU), CMP (82 HU), NP (65 HU) and EP (57 HU).
Tumor size measurements were taken on axial images in CMP, as the resolution is highest in this phase (Figure 7).

In the presence of multi-focal tumors, attenuation and size measurements were taken on the largest lesion.

**Statistical analysis**

Comparison of contrast enhancement between the phases was made with paired Student’s t-test: p-values $<0.05$ were considered significant. All analyses were performed with R software version 2.15.2 (73).

**Paper III**

Different preparation protocols were used during the study period, as patients in this study also participated in the comparison of different preparation protocols (Paper IV). Patients were asked to drink 500 or 1000 ml of fluid and not to void one or two hours before the examination.

For all patients, the post-contrast phases (CMP, NP, and EP) were separately randomized into an evaluation order, resulting in a list consisting of 318 different phases. Two experienced uroradiologists independently interpreted the phases retrospectively in the same order with axial and coronal reconstructions available for the phase analyzed. The reviewers were blinded to patient diagnosis, cystoscopy findings, original CTU reports, the other phases in the same examination, and the other reviewers result. Whether a bladder tumor was present or not was reported in a form. If a bladder tumor was present, the number of lesions and locations were reported to enable later verification that in fact the tumor was reported as tumor. One reviewer also rated the experienced confidence that the diagnosis was correct by marking a visual analogue scale (VAS) with the endpoints 0= 'not convinced at all’ and 10= 'could not be more convinced’.

The interpretation forms from both reviewers were compiled and compared by a third radiologist not involved in the CTU interpretations. The CTU interpretation reports were also compared with the cystoscopy findings and final diagnoses.

In patients with bladder cancer diagnosis, the CTU examination was reevaluated to measure tumor size (Figure 7). The shortest tumor diameter was considered the most relevant measurement as this part of the tumor usually protrudes into the bladder, as bladder tumors can grow flat. As this diameter should contribute the most to detecting the tumor during CTU, it was used in this study.
**Statistical analysis**

To compare performance measures between phases, the data from the two reviewers and the three phases were combined and separate logistic regression models for each performance measure were estimated. Generalized estimating equations were used to adjust for correlations of repeated measures within patients (74).

Wilcoxon's signed rank test was used to investigate differences in diagnosis confidence between phases.

A p-value <0.05 was considered a significant difference. All statistical analyses were performed with the software SAS, version 9.3 (SAS Institute, Cary, NC, USA).

**Paper IV**

Preparation protocol instructions regarding fluid intake and voiding restrictions were sent to the patients by mail and the preparations were made before they arrived at the hospital. The four different preparation protocols are presented in Table 4.

<table>
<thead>
<tr>
<th></th>
<th>Fluid intake instructions</th>
<th>Voiding restrictions</th>
<th>Furosemide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drink 500 ml of fluid during the one-hour period before the examination.</td>
<td>Void one hour before the examination but not after that.</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Drink 500 ml of fluid during the one-hour period before the examination.</td>
<td>Void one hour before the examination but not after that.</td>
<td>10 mg IV immediately before the examination.</td>
</tr>
<tr>
<td>3</td>
<td>Drink 1000 ml of fluid during the two-hour period before the examination.</td>
<td>Void two hours before the examination but not after that.</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Drink 1000 ml of fluid during the two-hour period before the examination.</td>
<td>Void one hour before the examination but not after that.</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 4.**
The preparation protocols used.
The Volume program on a workstation (Multi Modality Workstation, version VE30A, Siemens Forchheim, Germany) was used and the bladder wall was manually marked with the free-hand ROI tool when bladder volume was calculated from axial images (Figure 9). The evaluation limits were 40 HU (upper limit) and –40 HU (lower limit).

Bladder distension evaluation was made in CMP by rating distension as “satisfactory” or “not satisfactory”. Satisfactory was defined as a bladder wall being convex in both the axial and coronal planes, allowing reliable evaluation of the bladder (Figures 10 and 11).

Bladder distension was evaluated without prior knowledge of which preparation protocol the patient had followed. The calculations of bladder volume were made by the same radiologist who evaluated the bladder distension, but at a different time point.

Between CMP and EP and while the patients were on the examination table, they were asked about compliance with fluid intake and voiding.
restrictions by a nurse, who also helped the patients complete a questionnaire to obtain a high response rate. If the patient had not complied with the instructions, they were asked to state why. The patients were also asked to rate the desire to void at the time of the CTU examination through a visual analogue scale (VAS) (75) with the endpoints 0= ‘no desire to void’ and 10= ‘painful and unbearable desire to void’. A follow-up questionnaire, also with VAS, about the patients’ desire and need to void <1 h, 1–3 h, 3–6 h and 6–24 h post-examination was given to the patient after the examination and was to be completed at home and sent by mail to the hospital in an enclosed prepaid, pre-addressed envelope.

**Figure 10.**
Example of bladder sufficiently distended to allow evaluation. The bladder walls are convex: axial (A) and coronal (B) planes.

**Figure 11.**
Example of bladder not sufficiently distended to allow evaluation. The bladder walls are not convex: axial (A) and coronal (B) planes.
Patients not complying with the instructions on fluid intake and voiding restrictions were excluded from the analyses of bladder distension and experience of voiding at the time of examination. Patients not complying with the instructions on fluid intake were also excluded from analyses of experience after the examination.

**Statistical analysis**

The Mann Whitney test was used for pairwise comparisons of bladder volume and desire to void for the four groups. Student’s t-test was used to analyze bladder volume in patients with satisfactory bladder distension and not satisfactory bladder distension. Fisher’s exact test was used to compare the number of bladders sufficiently distended to evaluate, and the instruction compliance in the four groups. P-values <0.05 were considered significant.
Results

Paper I

Bladder cancer was the final diagnosis in the medical records of 54 of the 435 patients. During the follow-up period, four additional patients were registered with bladder cancer diagnosis in the cancer register. Two of these patients were originally diagnosed with tumors in the renal pelvis or ureter that were detected with CTU. The bladder tumors detected two and six years later, were metachronous urothelial tumors and not considered missed bladder tumors at the primary investigation. The third patient presented with gross hematuria five years after the primary episode. Primarily, both CTU and cystoscopy results for this patient were negative. At the second gross hematuria episode only flexible cystoscopy was performed and two small tumors, 3 and 4 mm in size, were detected. These tumors were considered new tumors and not bladder tumors missed at the primary investigation. The fourth patient underwent a second gross hematuria investigation two years after the primary gross hematuria episode. At CTU, a 16 mm tumor was detected, and retrospectively, a 4 mm tumor could be located in the same location in the primary CTU examination. This tumor was considered a missed bladder tumor at the primary investigation (Figure 12).

Thus, in total, 55 patients were diagnosed with bladder cancer.

Figure 12.
A bladder tumor (arrows) that was missed at the primary gross hematuria investigation: CMP (A) and EP (B). The tumor was detected two years later: CMP (C) and EP (D).
**Tumor size**
Median tumor diameter in the axial plane was 18 mm (range 4–56 mm).

**CTU**
The tumors were detected and described in the CTU examination report for 48 patients (87%). For 16 patients, the radiologist knew a bladder tumor or suspected bladder tumor was detected at cystoscopy. When these cases were excluded from the calculations, CTU detected bladder tumor in 35 of the remaining 39 patients (90%).

The CTU examination report incorrectly indicated tumors in five patients (false positives). One patient had a general thickening of the bladder wall but no distinct contrast enhancement: the diagnosis was infection and cystoscopy verified inflammation in the bladder wall. One patient had a suspicious urachal tumor with a discreet focal thickening of the ventral cranial aspect of the bladder wall, but further examinations, including cystoscopy, in addition to absence of progress over time, eliminated this diagnosis. One patient had a blood clot in the bladder and bladder tumor was mentioned as a differential diagnosis that had to be eliminated. Two patients had prostate hyperplasia and irregular thickening of the bladder without distinct contrast enhancement near the prostate.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for bladder cancer detection with CTU is presented in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>CTU</th>
<th>Flexible cystoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.87</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.99</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>0.91</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>0.98</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 5.
Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for bladder cancer detection with CTU and flexible cystoscopy.
In the retrospective analysis of the CTU examination, four additional tumors were detected (Figure 13), resulting in 52 (95%) tumors detected with CTU. The tumors found retrospectively were smaller (median tumor diameter 6.5 mm (range 4–13 mm)) than the tumors correctly diagnosed in the primary investigation (median tumor diameter 19.5 (range 7–56 mm)), and were not included in the calculations.

Three tumors were not detected, primarily or retrospectively, with CTU. One tumor was a CIS and the diagnosis was made from mapping biopsies at cystoscopy. This patient was additionally diagnosed with a distal ureter cancer that was detected with CTU and the ureter cancer probably caused the gross hematuria. One tumor was missed at both CTU and cystoscopy, but the malignant cells were identified by cytology and the tumor could be detected and treated at a second cystoscopy with rigid cystoscope combined with TUR-B. One was a 3 mm exophytic tumor detected with flexible cystoscopy; with CTU only a small area with modestly increased contrast enhancement in the bladder wall was seen, but no distinct tumor.

Figure 13.
Example of a retrospectively detected bladder tumor (arrows) near the right ostium in axial plane in CMP (A) and EP (B), and in coronal plane in CMP (C) and EP (D). This 22-year-old patient must be assumed to have good cardiovascular function with fast blood circulation, which could explain the suboptimal late scan of the CMP (equal contrast material concentration in the arteries and veins). The suboptimal CMP scan leading to suboptimal contrast material enhancement in the tumor could possibly explain why the tumor was missed primarily.
**Flexible cystoscopy**

Flexible cystoscopy found tumors in 48 (87%) of the 55 patients. In nine cases, the urologist performing the cystoscopy examination knew a bladder tumor had been detected or suspected with CTU. When these cases were excluded from the calculations, flexible cystoscopy detected tumors in 40 of the 46 remaining patients (87%).

In one patient, the cystoscopy was reported as “suspected bladder cancer”, but the final diagnosis was infection. This case is considered as false positive.

Sensitivity, specificity, PPV, and NPV values for flexible cystoscopy are presented in Table 5.

Seven tumors were not detected with flexible cystoscopy. In two patients, bladder evaluation with cystoscopy was impossible due to massive hemorrhage (Figure 14). In two patients, the tumors were detected at a second cystoscopy with guidance of the CTU results (Figure 15). In one patient CIS was diagnosed from mapping biopsies during cystoscopy. This patient was diagnosed additionally with a distal ureter cancer that was detected with CTU and it was probably the ureter cancer that caused the gross hematuria. In one patient the tumor was missed both at the primary cystoscopy and CTU, but cytology identified the malignant cells and the tumor could be detected and treated at a second cystoscopy with rigid cystoscope combined with TUR-B. In one patient, the primary gross hematuria investigation including both CTU and cystoscopy was negative and the tumor was detected two years later (Figure 12).
Figure 14.
Example of a large tumor (arrows) in the right aspect of the bladder causing massive hemorrhage making evaluation of the bladder with cystoscopy impossible. Axial plane in CMP (A) and EP (B). Coronal plane in CMP (C) and EP (D).

Figure 15.
Example of a tumor (arrows) located in the right aspect of the bladder missed at the primary cystoscopy, but detected at a second cystoscopy after the tumor was detected with CTU. Coronal plane in CMP (A) and EP (B).
Paper II

Tumor attenuation
In 96% of the tumors, contrast enhancement was 20 HU or more. The attenuation and enhancement values in the different phases are presented in Table 6, the enhancement pattern in all patients is presented in Figure 16, and the enhancement distribution in CMP, NP, and EP is presented in Figure 17.

Table 6.
Mean ± 1 SD (range) attenuation and enhancement values in HU in the tumors. Enhancement was calculated as the attenuation in HU in CMP, NP, or EP, minus the attenuation in HU in UE.

<table>
<thead>
<tr>
<th>Phase</th>
<th>UE</th>
<th>CMP</th>
<th>NP</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuation</td>
<td>40±8  (15–58)</td>
<td>77±14  (45–110)</td>
<td>64±8  (53–80)</td>
<td>57±11  (25–86)</td>
</tr>
<tr>
<td>Enhancement</td>
<td>-</td>
<td>37±13  (15–75)</td>
<td>25±8  (10–40)</td>
<td>17±9  (0–45)</td>
</tr>
</tbody>
</table>

Figure 16.
Enhancement pattern in all patients. Contrast enhancement in HU on the y-axis and post-contrast phases on the x-axis. Mean values are marked in bold red.
Figure 17.
Enhancement distribution in CMP (A), NP (B), and EP (C). Contrast enhancement in HU on the x-axis and number of patients on the y-axis. Mean values marked in red.
The mean difference (95% confidence interval) in contrast enhancement was 11.2 HU (6.25–16.2 HU) between CMP and NP; 20.4 HU (16.0–24.8 HU) between CMP and EP; and, 8.4 HU (4.81–11.9 HU) between NP and EP.

Contrast enhancement was higher in CMP than in both NP (p<0.001) and EP (p<0.001). Mean contrast enhancement was higher in NP than in EP (p<0.001).

The highest contrast enhancement in CMP was seen in 44 of the 50 patients (88%). Equal contrast enhancement in CMP and EP was seen in three patients (6%) and the highest contrast enhancement in EP was seen in three patients (6%).

Among the patients undergoing the four-phase protocol, the highest contrast enhancement in CMP was seen in 17 of 21 patients (81%). Equal enhancement in the CMP and NP was seen in three patients (14%); in one of these patients, the enhancement remained equal in EP. In one patient (5%), the highest contrast enhancement was seen in EP, then CMP and NP.

**Tumor size**
The mean value ± 1 SD of the smallest diameter of the bladder tumors in the axial reconstructions was 22±12 mm (range 5–56 mm).

**Paper III**

**Tumor size**
The median tumor diameter measured in axial plane was 17 mm (range 5–40 mm).

**CTU interpretation**
The interpretation results from reviewer 1 and 2 for patients with bladder tumors are presented in Table 7, and the interpretation results for patients without bladder tumors are presented in Table 8.

Both reviewers had the highest detection rate of bladder tumors per patient in CMP (20/21). Reviewer 1 had a slightly higher detection rate in NP (18/21) than in EP (17/21). Reviewer 2 had the same detection rate in both NP and EP (17/21).
Table 7.
CTU interpretation results in all phases from both reviewers for patients with bladder tumor diagnosis (n=21). “Yes” meaning tumor detected and “No” meaning tumor not detected. Correct interpretation marked in bold.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Reviewer 1</th>
<th>Reviewer 2</th>
<th>Frequency (n=21)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMP</td>
<td>Yes</td>
<td>Yes</td>
<td>19</td>
<td>90.48</td>
</tr>
<tr>
<td>CMP</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>4.76</td>
</tr>
<tr>
<td>CMP</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>4.76</td>
</tr>
<tr>
<td>CMP</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NP</td>
<td>Yes</td>
<td>Yes</td>
<td>16</td>
<td>76.19</td>
</tr>
<tr>
<td>NP</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>9.52</td>
</tr>
<tr>
<td>NP</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>4.76</td>
</tr>
<tr>
<td>NP</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>9.52</td>
</tr>
<tr>
<td>EP</td>
<td>Yes</td>
<td>Yes</td>
<td>15</td>
<td>71.43</td>
</tr>
<tr>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>9.52</td>
</tr>
<tr>
<td>EP</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>9.52</td>
</tr>
<tr>
<td>EP</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>9.52</td>
</tr>
</tbody>
</table>

Table 8.
CTU interpretation results in all phases from both reviewers for patients without bladder tumor diagnosis (n=85). “Yes” meaning tumor detected and “No” meaning tumor not detected. Correct interpretation marked in bold.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Reviewer 1</th>
<th>Reviewer 2</th>
<th>Frequency (n=85)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMP</td>
<td>No</td>
<td>No</td>
<td>76</td>
<td>89.41</td>
</tr>
<tr>
<td>CMP</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
<td>5.88</td>
</tr>
<tr>
<td>CMP</td>
<td>Yes</td>
<td>No</td>
<td>2</td>
<td>2.35</td>
</tr>
<tr>
<td>CMP</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>2.35</td>
</tr>
<tr>
<td>NP</td>
<td>No</td>
<td>No</td>
<td>80</td>
<td>94.12</td>
</tr>
<tr>
<td>NP</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>3.53</td>
</tr>
<tr>
<td>NP</td>
<td>Yes</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NP</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
<td>2.35</td>
</tr>
<tr>
<td>EP</td>
<td>No</td>
<td>No</td>
<td>80</td>
<td>94.12</td>
</tr>
<tr>
<td>EP</td>
<td>No</td>
<td>Yes</td>
<td>4</td>
<td>4.71</td>
</tr>
<tr>
<td>EP</td>
<td>Yes</td>
<td>No</td>
<td>1</td>
<td>1.18</td>
</tr>
<tr>
<td>EP</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Tumors in eight patients were missed in one or more phases by one or both reviewers.

In CMP, tumors were missed by the reviewers in one patient each. In one patient, the tumor was 18 mm and located near one of the ureter ostiums, and in the other patient, there were two tumors, with smallest diameter of 5 mm, located in the ventral aspect of the bladder: these 5 mm tumors were only detected in CMP (Figure 18).

In NP, reviewer 1 missed tumors in three patients and reviewer 2 missed tumors in four patients. Tumors in two patients were missed by both reviewers; in one patient, there was a 20 mm tumor located in the cranial aspect of the bladder (Figure 19) and in the other patient, there were 5 mm ventrally located tumors, also missed in CMP by one reviewer (Figure 18). Of the three remaining tumors, two were located near an

Figure 18.
Two tumors (arrows) with the smallest diameter of 5 mm located in the ventral aspect of the bladder in CMP (A), NP (B), and EP (C). These tumors were only detected in the CMP.
ostium and measured 10 and 18 mm, and one was a 20 mm tumor located in the right aspect of the bladder, which was not sufficiently distended. The median size of the tumors missed in five patients in NP was 18 mm (range 5–20 mm).

In EP, the reviewers missed tumors in four patients each, and in two patients, the tumors were missed by both reviewers. One was 18 mm and located near one ostium; this was also missed by one reviewer in CMP and one reviewer in NP. In the other patient, the tumors missed were 5 mm; these tumors were also missed by one reviewer in CMP and both reviewers in NP (Figure 18). The four remaining tumors missed in EP were in different patients. Two tumors were located in the left aspect of the bladder and did not show as filling defects because of layering of the contrast material in the bladder, one was a 10 mm tumor located near an

**Figure 19.**
The 20 mm tumor (arrows) missed by both reviewers in NP, but detected by both reviewers in CMP and EP. Coronal plane in CMP (A), NP (B), and EP (C).
ostium, and one was a 12 mm tumor in an insufficiently distended bladder. The median size of the tumors missed in six patients in EP was 11 mm (range 5–18 mm).

The number of false positive findings was higher in CMP (n=11) than in NP (n=7) and in EP (n=5). In both CMP and NP, two cases of false positive findings were mutual for the reviewers, whereas, in EP, all cases of false positive findings were in different patients. The most common false positive finding was an enlarged irregular prostate (Figure 20). Other examples of false positive findings were focal thickening of the bladder wall, blood clots or urinary calculi in the bladder, and in EP, a jet from

![Figure 20.](image)

*Figure 20.*
Example of an irregularly bulging enlarged prostate, the most common false positive finding. CMP (A), NP (B), and EP (C) in axial and coronal planes.
the ureter that generated a heterogeneous mix of contrast material and non-opacified urine that was mistaken for a filling defect and tumor.

The merged values for both reviewers for sensitivity, specificity, PPV, and NPV for bladder tumor detection per patient in the different phases are presented in Table 9.

The sensitivity for bladder tumor detection per patient was higher with CMP than with NP (p=0.016) or EP (p=0.0003). There was no difference in sensitivity between NP and EP.

The specificity for bladder tumor detection per patient was higher in EP than in CMP (p-value 0.035). There was no difference in specificity between CMP and NP, or between NP and EP.

There was no difference in PPV between the phases.

However, NPV was higher for CMP than for both NP (p=0.024) and EP (p=0.002). There was no difference in NPV between NP and EP.

The diagnose confidence rating is presented in Figure 21. The median value for experienced confidence was highest in CMP (8.4), then NP (7.7) and EP (6.5). The difference was significant between CMP and both NP (p=0.004) and EP (p<0.0001), and between NP and EP (p<0.0001). The confidence rating was higher when the diagnosis was correct than when it was incorrect (Figure 22) in CMP (p=0.039) and NP (p=0.002). However, there was no difference between correct and incorrect diagnoses in the EP.

Table 9.
Merged sensitivity, specificity, PPV and NPV values (95% confidence interval) in CMP, NP, and EP.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Accuracy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMP</td>
<td>0.95 (0.83–0.99)</td>
<td>0.94 (0.88–0.97)</td>
<td>0.78 (0.62–0.89)</td>
<td>0.99 (0.95–1.0)</td>
<td>0.94 (0.89–0.97)</td>
</tr>
<tr>
<td>NP</td>
<td>0.83 (0.65–0.93)</td>
<td>0.96 (0.90–0.98)</td>
<td>0.83 (0.64–0.93)</td>
<td>0.96 (0.90–0.98)</td>
<td>0.93 (0.88–0.97)</td>
</tr>
<tr>
<td>EP</td>
<td>0.81 (0.63–0.91)</td>
<td>0.97 (0.93–0.99)</td>
<td>0.87 (0.72–0.95)</td>
<td>0.95 (0.90–0.98)</td>
<td>0.94 (0.89–0.97)</td>
</tr>
</tbody>
</table>
Figure 21.
Rating of experienced confidence that the diagnosis was correct in CMP, NP, and EP. Median values with interquartile range (IQR), 1.5 IQR, and outliers marked.

Figure 22.
Confidence rating when the diagnosis was correct and incorrect in CMP, NP, and EP. Median values with interquartile range (IQR), 1.5 IQR, and outliers marked.
Paper IV

Part 1: Ability to follow preparation protocol

Patient compliance with the preparation protocol: instructions on fluid intake and restrictions in voiding is presented in Figure 23.

In Group 2, 22 of 25 patients (88%) were able to follow the preparation protocol and in Group 4, 14 of 25 patients (56%). There was a difference in compliance between Groups 2 and 4 (p=0.0025).

No difference was found when analyzing the fluid intake instructions and voiding restrictions separately.

Patients not complying with the fluid intake instructions reported they either did not have enough time (n=5) or felt the amount of fluid was too great (n=4). Patients who did not follow the voiding restrictions reported they were either incontinent (n=3) or had too much discomfort owing to the urge to void (n=8).

The instructions on fluid intake and voiding restrictions were easy to understand for 22 patients (88%) in Group 1, 19 (76%) in Group 2, 17 (68%) in Group 3, and 21 (84%) in Group 4.

Figure 23.
Patient compliance with the different preparation protocols. All patients are included.
Part 2: Bladder distension and volume

The number of patients with bladders sufficiently distended to permit confident bladder evaluation and bladder volume in the different groups are presented in Table 10.

There was no difference between the groups in number of bladders with satisfactory distension.

Patients in Group 1 had smaller bladder volume than patients in Group 2 (p=0.027) and Group 3 (p=0.016).

Patients with bladders evaluated with satisfactory distension had larger bladder volumes (mean 387.7±200 ml: range 147–1108 ml) than patients with bladders evaluated not to have satisfactory distension; (mean 113.9±37 ml: range 41–176 ml), p<0.001.

Table 10.

Evaluation of bladder distension and calculation of bladder volume. Only patients who complied with the preparation protocol for both fluid intake and voiding restrictions were included.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Bladder distension</th>
<th>Bladder volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Satisfactory</td>
<td>Unsatisfactory</td>
</tr>
<tr>
<td>1</td>
<td>10 (56%)</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>16 (72%)</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>14 (82%)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>11 (78%)</td>
<td>3</td>
</tr>
</tbody>
</table>

Part 3: Patient discomfort

The urge to void during the CT examination is presented in Table 11.

The urge to void during the CT examination was lowest for patients in Group 1 and highest in Group 2, and there was a difference between these groups (p=0.002). All patients answered the questions regarding the urge to void during the CT examination.

The urge to void after the CT examination is presented in Figure 24.

Response rate to the questionnaire regarding the urge to void post-examination was 92 out of 100; 23 in group 1, 23 in group 2, 22 in group 3, and 24 in group 4.
Table 11.
Urge to void during the CT examination. 0 = ‘no urge at all to void’ and 10 = ‘painful urge to void’. Only patients who were able to follow the preparation instructions for both fluid intake and voiding restrictions were included.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Urge to void, median (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 (0–7)</td>
</tr>
<tr>
<td>2</td>
<td>5.5 (0–10)</td>
</tr>
<tr>
<td>3</td>
<td>3.5 (0–10)</td>
</tr>
<tr>
<td>4</td>
<td>5.0 (0–9.2)</td>
</tr>
</tbody>
</table>

Figure 24.
Patients desire and need to void during the 24-hour period post-CT-examination, median values. 0 = ‘no or normal desire and need to void’ and 10 = ‘unbearable desire and need to void’. Patients not complying with the instructions for fluid intake were excluded.
Within the first hour post-examination, patients in Group 2 had a greater urge to void than patients in both Group 1 (p=0.003) and Group 3 (p=0.035). During 1–3 hours post-examination, Group 2 also had a greater urge to void than Group 3 (p=0.009). During 3–6 and 6–24 hours post-examination, there was no difference between the groups.
Discussion

Bladder tumor is the most common tumor detected in patients presenting with gross hematuria and is a heterogeneous disease with great variation in malignancy grade. Although good prognosis relies on early diagnosis and treatment (21, 22), delay in both diagnosis and treatment of bladder cancer is common (23-25).

CTU plays a central role in bladder cancer evaluation (47, 48). If a bladder tumor is detected with CTU, the patient can be referred immediately for a rigid cystoscopy with simultaneous resection; this reduces the number of flexible cystoscopy examinations. With bladder cancer detection with CTU, delay in diagnosis and treatment could be reduced as flexible cystoscopy in these patients is by-passed; thus prognosis may be improved. Furthermore, if the CTU protocol is designed for tumor detection and staging in one single examination, this could further contribute to reducing delay in diagnosis and treatment because multiple examinations become unnecessary. The ability to detect bladder tumors with CTU has improved and if the sensitivity for bladder cancer detection with CTU is comparable with, or better than, the sensitivity of flexible cystoscopy, patients with normal CTU findings can be spared cystoscopy.

Paper I

With our CTU protocol, the sensitivity (0.87), specificity (0.99), PPV (0.91), and NPV (0.98) for detecting bladder tumors were comparable to other studies where the bladder is assessed filled with contrast material (46) or in a contrast enhancing phases (49, 51); where sensitivity of 0.83-0.95, specificity 0.89-0.94, PPV 0.71-0.94, and NPV 0.87-0.97 are found (46, 49, 51). The detection rate with CTU increased from 87% to 90%, and remained at 87% with flexible cystoscopy, when patients with known or suspected bladder tumors were excluded. As bladder cancer detection rate for both CTU and flexible cystoscopy, were not negatively affected by excluding cases with known or suspected bladder tumors, these patients were included in the calculations.

In studies where the bladder is assessed in early contrast enhancing phase (49, 51), fixed time delays of 60 or 70 s are used after a 100-160 ml injection of contrast material (300-320 mg I/ml) at a rate of 3 ml/s. In our study, a higher injection rate (4 ml/s) and a smaller quantity of contrast material (60-80 ml) with higher concentration (350 mg I/ml) were used, which gave an earlier and more intense, but shorter, contrast enhancement peak (35). Current CT scanners are sufficiently fast to catch the peak, and the use of a ROI that measures and follows the con-
Contrast enhancement improves the precision of the scan during that peak, regardless of the patient’s cardiovascular function (57, 58). Patients with gross hematuria are generally older (5) and at risk of reduced kidney function; thus, a smaller quantity of contrast material is beneficial when examining these patients.

The original CTU reports were evaluated to determine the ability for detecting bladder tumors, as bladder tumors must be detected during the daily workflow in order to reduce delay to diagnosis and treatment and possibly improve prognosis by directing patients to rigid cystoscopy and resection.

Four bladder tumors missed by flexible cystoscopy were detected with CTU, two of which were found at a second cystoscopy with a rigid cystoscope after guidance from the CTU examination. One tumor was detected with flexible cystoscopy, but missed at CTU. Two tumors (one of them CIS) were detected by mapping biopsies and cytology. If CTU would have been the primary examination for patients presenting with gross hematuria, then 53 patients (patients with true or false positive CTU findings for bladder tumor) could have been referred directly for rigid cystoscopy (47, 48). This would have resulted in 12% reduction in flexible cystoscopy examinations. However, five of the 53 patients did not have a bladder tumor and would have undergone rigid cystoscopy unnecessarily.

The four tumors detected retrospectively, resulting in totally 52 tumors detected, demonstrated bladder tumor detection with CTU in the daily workflow could be improved. If these tumors are included in the calculations, sensitivity would increase to 0.95, whereas, the other parameters would remain unchanged. The combination of CTU and flexible cystoscopy detected 52 out of 55 tumors. If only CTU was the primary examination in patients presenting with gross hematuria, and all detectable tumors were detected primarily, then, bladder tumor in three patients would have been missed. One of these patients was diagnosed with CIS in addition to a distal ureter cancer, which was detected with CTU and was the probable cause of the gross hematuria. The two remaining patients had exophytic but small tumors that were not detected with CTU and did not have any additional diagnoses. From the original 435 patients presenting with gross hematuria, the bladder cancer diagnosis
would be missed by CTU in these two patients (0.5%). It is unlikely the gross hematuria would stop and the patients would probably return, as was the case with the patient whose tumor was missed by both CTU and cystoscopy at the primary investigation (Figure 12). This suggested that sparing selected patients a cystoscopy examination could be considered if the CTU examination is negative after a primary gross hematuria episode. However, the CTU examination must be adapted for, and permit, adequate bladder assessment. Flexible cystoscopy is an invasive examination that is inconvenient and involves an increased risk of infection, but in cases of recurrent gross hematuria and repeated normal CTU examinations, flexible cystoscopy should be performed.

Cystoscopy had a sensitivity of 0.87, specificity of 1.0, PPV of 0.98 and NPV of 0.99, which was comparable to other studies (sensitivity 0.96-0.98; specificity 0.94; PPV 0.65-0.8; and, NPV 0.99-1.0 (46, 47, 54)).

The biggest difference between CTU and flexible cystoscopy was for PPV (0.91 for CTU and 0.98 for flexible cystoscopy), which could be explained by the higher number of false positives with CTU. In some cases, bladder tumor was one of the differential diagnoses that had to be excluded, e.g. blood clot in the bladder or thickening of the bladder wall due to inflammation. This over-diagnosing with CTU is necessary, as biopsy cannot be taken with CTU. For both CTU and flexible cystoscopy, sensitivity was the same (0.87), as was NPV (0.98). Specificity was slightly higher for flexible cystoscopy (1.0) than for CTU (0.99).

Although the work-up protocol for gross hematuria included both CTU and flexible cystoscopy, at the time of data collection, there were no guidelines about the order the examinations should be performed. As the intention of CTU is for guiding bladder tumor patients directly to rigid cystoscopy, CTU must be performed as the primary investigation. Hence, patients undergoing TUR-B and biopsy before CTU were not relevant in the study and were excluded.

Patients (n=53) with unknown cystoscopy results were excluded from the study. For these patients, there was either another explanation for the gross hematuria, e.g. renal tumor or urolithiasis, or they were lost to follow-up, as the referring unit was a private clinic with a separate medical journal record system.
Paper II

Bladder tumors contrast-enhance (96% of the tumors had an enhancement of 20 HU or more) and the majority of the tumors (88%) were found to have highest enhancement in CMP. A quick washout in the tumors was observed with a decrease in mean enhancement from CMP (37 HU) to NP (25 HU), and an additional decrease to EP (17 HU).

In a study (52) of 20 patients with bladder tumors, with size 1.5 cm or more, diagnosed by cystoscopy before CT examination, 85% of the tumors contrast enhanced maximally on 60 s delay scans. Although the scans over the bladder had fixed delay times of 40, 60, 80 and 100 s after contrast material injection at a rate of 4 mL/s, the quantity of contrast material injected varied and there was no information on contrast material concentration. The contrast peak must be presumed to differ as there was variation in both the amount of contrast material used and the heart function of the patients, which has been previously discussed (51). The present CTU protocol was individually adjusted because the use of ROI triggered the start of the CMP scan. The CMP started with a delay of 25 – 45 s and as the scan was performed in the craniocaudal direction, the bladder was examined almost 10 or 15 s later. Consequently, the bladder was examined with a delay of approximately 35 – 60 s. As most patients were elderly (mean age 70 years), they were probably examined with a delay closer to 55 – 60 seconds as cardiovascular function usually decreases with age.

Attenuation in the tumors was measured on the 3 mm axial reconstructions. Partial volume effect can result in false attenuation values, especially when measuring attenuation in small tumors (the smallest tumor was only 5 mm in short dimension), despite the effort to maintain the ROI in the middle of the tumor. In CMP and NP, the non-enhanced urine surrounding the tumor could result in a falsely low attenuation value, and in EP, the contrast-blended urine surrounding the tumor could result in a falsely high attenuation value. With a lobulated tumor, this would be accentuated. In small tumors, attenuation values can be assumed a little higher in CMP and NP, and a little lower in EP. However, falsely low attenuation values should be equal in both CMP and NP, and the difference in attenuation between these phases must be considered unchanged.

The shortest dimension was chosen for reporting tumor size as this dimension was assumed to have the greatest affect on attenuation values and tumor detection. The highest contrast enhancement was usually in CMP. However, in 3 patients, the highest enhancement was in EP. In these cases, the tumor size was smaller than average (between 8 and 11 mm), and in the smallest tumor, the highest enhancement was in EP and lowest enhancement was in NP. Therefore, it must be assumed the partial volume effect combined with image noise, because of relatively
low radiation dose in EP, can make attenuation measurements uncertain, especially in small tumors.

Although all tumors with histopathological data (49/50) were UCC, the attenuation and enhancement values still varied considerably (Table 1 and 2). This could not be explained by differences in tumor type, and must be assumed to derive from differences in vascularization: as bladder tumors vary in vascularization (76). In one patient with a bladder tumor over 6 cm on CTU, there were no histopathological data because the hemorrhage from the tumor was profuse during cystoscopy rendering biopsy impossible. The diagnosis was accepted by both urologists and oncologists.

In patients aged 50 years or more, the routine CTU protocol included NP in addition to UE, CMP, and EP. As only 21/48 patients aged 50 or more with bladder tumor underwent the four-phase protocol, this is a limitation to this study. The actual reason for the low number undergoing the four-phase protocol was uncertain, but could be due to several factors. The CTU protocol used for patients under the age of 50 years (UE, CMP and EP) was preselected in the CT scanner to avoid examining these patients with the four-phase protocol. Therefore, with patients aged 50 years or more, the CTU protocol must be actively changed. If a new radiographer or a student (the hospital is a teaching hospital) unfamiliar with the routine of changing the protocol for patients aged 50 or more, performed the examination, the changing of the protocol could have been missed. Lack of time and stress, common elements in a radiographer’s work situation, could not be excluded.

After TUR-B or biopsy, there is an inflammatory response to the treatment in the bladder wall. Despite the possibility of a remaining tumor after TUR-B or biopsy, these patients were excluded, as it was not possible to differentiate between contrast enhancement in the tumor and contrast enhancement in the inflammatory tissue post treatment. Most patients that underwent a TUR-B or biopsy were patients with bladder tumors, thus, many patients with bladder tumor were excluded. Similarly, patients with a previous history of treated bladder cancer were excluded, as the treatment, consisting of e.g. multiple TUR-B, chemotherapy and BCG installations, radiation treatment and partial resection of the bladder were presumed to alter the enhancement pattern and affect the bladder wall. However, despite CTU findings, these patients are always examined with cystoscopy.

Patients whose bladders were not possible to evaluate at CTU, such as patients with hip prosthesis that give artifacts in the area of the bladder, were excluded, as these bladders could not be assessed by either excre- tory or contrast enhancing phase.
Paper III

The CTU protocol must be designed to detect bladder tumors in as many patients as possible. High sensitivity and NPV values are important for directing patients with bladder tumor to rigid cystoscopy. Thus, only per patient calculations were made because the main intention with the CTU examination should be to refer patients with bladder tumors directly to rigid cystoscopy, irrespective of the number of tumors detected.

Sensitivity was higher in CMP (0.95) than in both NP (0.83) and EP (0.81), and NPV was higher in CMP (0.99) than in NP (0.96) and EP (0.95).

The higher specificity in EP (0.97) than in CMP (0.94) was explained by the higher number of false positive findings in CMP than in EP. The assessment of CTU examinations in the daily workflow includes the interpretation of all phases in the CTU protocol. The detection of 20/21 tumors, with three false positive findings in the original clinical interpretation, resulted in a sensitivity of 0.95, a specificity of 0.96, PPV of 0.87, and NPV of 0.99. However, each phase was evaluated individually in the study, and the confidence rating was higher when the diagnosis was correct than when incorrect. The number of false positive findings could be reduced if the information from all phases in the examination is combined. If reviewers had access to both UE and the post-contrast phase evaluated, contrast enhancement (52, 77), which is important for diagnosing bladder cancer, could have been measured. The lack of access to UE in the assessment of the post-contrast phases was a limitation to this study.

The EP in our CTU protocol was not optimized for bladder tumor detection as diuretics were not administered to all patients and the patients did not exercise before the EP scan. However, exclusion of EP from the CTU protocol was never considered as this phase contributes other diagnostic information, e.g. ureter anatomy, renal function, and relation between any neoplasms and the collective system (36, 78).

The NP is used for similar purposes as CMP, and as the sensitivity and NPV values of bladder tumor detection was higher in CMP than in NP, this phase could be excluded for patients 50 years or older to reduce radiation doses without losing diagnostic information (36).

In NP, a lower mAs was used (mAs 80) than in CMP (mAs 120), which could influence image quality and possibly bladder tumor detection. However, it was more likely the higher bladder tumor detection in CMP was a result of the higher contrast enhancement in the bladder tumors during CMP than during NP (Paper II (77)). As most tumors were
detected with CMP, the higher contrast enhancement in tumors in this phase was probably beneficial for detecting small bladder tumors: the smallest tumor (5 mm) located ventrally in the bladder was only detected in CMP (Figure 18).

For bladder tumor detection with UP, Metser et al (49) found a sensitivity of 0.89, specificity of 0.89, PPV of 0.91, and NPV of 0.87 in patients with known urothelial tumors or positive cytology but negative cystoscopy results. Park et al (51) had a sensitivity of 0.95, specificity of 0.91-0.93, PPV of 0.92-0.94, and NPV of 0.94 for detecting bladder cancer with a fixed delay scan of 70 s over the bladder in patients presenting with gross hematuria or recurrent microscopic hematuria. However, only patients undergoing both CTU and cystoscopy were included (25% of all patients undergoing CTU) and the bladders were controlled to be spherical and have a minimum diameter of 8 cm (51).

Our result with sensitivity of 0.95 with CMP was slightly higher than the result obtained by Metser et al (49), but comparable to Park et al (51), despite all patients, irrespective of bladder diameter, being included. However, our NPV value of 0.99 with CMP was higher than the NPV obtained by both Metser et al (49) (NPV 0.87) and Park et al (51) (NPV 0.94).

Our results with high sensitivity and NPV values were possibly explained by the enhancement-triggered start of the CMP, which increased the precision of the scan during the enhancement peak, irrespective of the patient’s cardiovascular function (57, 58). Thus, the majority of bladder tumors must be presumed to have adequate contrast enhancement, which should be beneficial for tumor detection.

In the study by Sadow et al (46), the bladder was assessed in EP, and a sensitivity of 0.83 for bladder tumor detection was obtained in patients with gross hematuria. This is comparable to our results with a sensitivity of 0.81 with EP.

Patients who had undergone biopsy or TUR-B before CTU were excluded, as it is not possible to differentiate post-treatment inflammatory tissue from bladder tumors.

A CTU protocol including UE, CMP, and EP allows simultaneous and effective tumor detection, staging, pre-operative planning, and anatomy evaluation. Consequently, this CTU protocol can contribute to reducing delay in bladder cancer diagnosis and treatment, partly by guiding patients directly to rigid cystoscopy and partly by making a complete pre-operative investigation in one primary examination.
Paper IV

There is no manifest preparation protocol for achieving sufficient bladder distension. The attempt to determine a preparation protocol that resulted in sufficient bladder distension for evaluation by CTU, was easy for the patient to follow, and did not cause discomfort, was difficult.

About one third of the patients could not follow the preparation protocol given to them; the voiding restrictions were particularly problematic. Group 4, where the patients were asked to drink 1 L of fluid during two hours, but void one hour before examination, had the lowest compliance. As in this protocol, the patients were asked to void in the middle of the preparation time, it can be considered to be somewhat more complicated than the other protocols. Group 3 had the highest mean age (68 years) and highest minimum age (55 years). In groups 1, 2, and 4, mean age was 58-62 years and minimum age was 18-25 years. As the highest mean age was not in the group with the lowest compliance, the age differences between the groups were not considered to influence compliance results. The preparations were made at home and as some patients had up to two hours travelling time to the hospital, it could be difficult to follow the drinking or voiding instructions while travelling.

A convex bladder wall due to proper distension of the bladder was considered the most important factor for bladder assessment. To obtain both a subjective and objective measurement of the bladder, bladder distension was evaluated and bladder volume was calculated. Patients with satisfactory bladder distension had larger bladder volumes than patients with unsatisfactory bladder distension. Large bladder volume alone was not crucial for confident bladder assessment at CTU, but was considered a subjective evaluation. Larger bladder volume meant there was greater possibility of proper bladder distension resulting in convex bladder walls, which were necessary for confident bladder assessment. Protocol 1, with an intake of 500 ml fluid during one hour, resulted in the highest number of patients with unsatisfactory bladder distension. However, there was no significant difference compared with the other groups. Group 1 also had the smallest median bladder volume, and there was a significant difference compared with groups 2 and 3.

The patients in group 2 had the highest urge to void during the examination and within the first hour, 1-3 hours, and 3-6 hours post-examination, and were considered to suffer the most discomfort. There was a difference between groups 1 and 2 during the examination and within the first hour post-examination. Within the first hour and 1-3 hours post-examination, there was also a difference between groups 2 and 3. The injection of Furosemide was considered to result in increased diuresis that persisted for hours after the examination. Patients with gross hematuria are often men and elderly and it was possible they were more affected by
the Furosemide injection than younger patients are, as they often suffer from prostate hyperplasia and incontinence. The persisting increase of diuresis probably affects the patients in their ordinary life, and this is considered unacceptable.

Protocol 3 was chosen as our preparation protocol, as protocol 4 had the lowest compliance, protocol 1 resulted in too small bladder volumes, and protocol 2 caused the patients unacceptable discomfort.

The study on achieving sufficient bladder distension had several limitations. One was the small number of patients; 100 patients divided into four groups, each with 25 patients.

Another limitation was the trust in the information the patients gave in the questionnaire. Many patients reported they had followed the instructions in the preparation protocol but did not have satisfactory bladder distension; only 72% (51/71) of the patients reporting they had followed the preparation protocol had satisfactory bladder distension. For patients that reported they did not follow the instructions, 69% (20/29) had satisfactory bladder distension. If all patients are included, 71% (71/100) had satisfactory bladder distension. The proportion of patients with satisfactory bladder distension was about the same, irrespective of whether patients who reported they had not followed the instructions were included or excluded. Thus, it was questionable whether all patients provided correct information in the questionnaire. As the preparations were performed outside the hospital, it is not known whether patients actually followed the instructions about fluid intake and voiding. The patients might have felt obliged to state they had followed the preparation protocol when asked by a nurse during the examination. The reason the patients were asked the questions while they were on the examination table waiting for the EP was to achieve a high response rate; however, this could have resulted in patients giving incorrect information. One option for increasing compliance and emphasizing the importance of the preparations could be for the patients to make the preparations in the waiting room at the hospital. Thus, fluid intake could be monitored by a nurse in the waiting room, in the same way outpatients undergoing a CT examination of the abdomen receive oral contrast material. However, these options were not possible as the waiting rooms were too small and patients would not appreciate spending two additional hours at the hospital. In addition, a dedicated nurse for watching the patients in the waiting room increases costs. Placing an indwelling catheter in the bladder and filling the bladder with saline solution while the patient is on the examination table would result in satisfactory bladder distension, however, this option was not considered as it is time consuming and has increased risk of infection.
Conclusion

General
CTU including UE, CMP, and EP, where the start of the CMP scan is enhancement triggered, should be used for the primary investigation of patients presenting with gross hematuria to guide patients with bladder tumors directly to rigid cystoscopy. If the CTU protocol is adapted for bladder assessment, patients with normal CTU findings may not need to undergo cystoscopy. Patients should be instructed to drink 1 L of fluid and not void during the two-hour period prior the examination.

Specific

Paper I
The detection rate of bladder tumors for a CTU protocol, where the start of the scan is enhancement triggered, is high and comparable to cystoscopy results. The CTU protocol should be used as the first examination in patients presenting with gross hematuria, and to direct patients with bladder tumors directly for rigid cystoscopy. If the CTU examination is negative, selected patients can be spared a cystoscopy examination.

Paper II
In a CTU protocol including UE, CMP, NP, and EP and where the scan start is enhancement triggered, contrast enhancement is higher in CMP than in the other post-contrast phases.

Paper III
In a CTU protocol, where the start of the scan is enhancement triggered, the sensitivity and NPV values for bladder cancer detection are higher in CMP than in both NP and EP, demonstrating the CMP should be used for bladder assessment. The NP can be excluded from the protocol without losing diagnostic information.

Paper IV
Among the four protocols, three of which are equal for bladder evaluation, Protocol 3, where the patients are asked to drink 1 L of fluid during the two-hour period prior the examination and not to void during that period, is the simplest and causes the least discomfort to the patients.


Comments

Before the introduction of CTU, the urinary tract was examined with excretory urography, where the collecting system (renal pelvis, ureters and bladder), was evaluated when the kidneys excreted the contrast material. Tumors appeared as contrast defects or irregularities in the contrast material. Reliable evaluation of the bladder was not possible with excretory urography.

When excretory urography was replaced by CTU, the tradition of detecting tumors in the collecting system and the bladder as filling defects in the excretory phase, tended to remain routine.

CTU should be used to its full potential and not just as an advanced excretory urography. The high resolution images generated in the modern CT scanners allow detection of tumors in the entire urinary tract, including the bladder, as contrast-enhanced masses rather than filling defects.
Sammanfattning på svenska


Rutinmässig utredning av makroskopisk hematuri består av skiktröntgen av urinvägarna (CTU) och flexibel cystoskopi (urologerna använder ett instrument för att undersöka urinblåsan). Traditionellt sett har cystoskopi använts för att undersöka blåsan och CTU för att undersöka resten av urinvägarna. På senare tid har undersökningsmetoder förfinats och blåscancer upptäcks ofta vid CTU. Studier har visat att om CTU utförs som första undersökning vid utredning av makroskopisk hematuri, kan patienter med blåscancer som upptäcks med CTU remitteras direkt för cystoskopi med stelt cystoskop då man har möjlighet att diagnostisera och även behandla tumören om den är liten. På så sätt minskas antalet flexibla cystoskopiundersökningar som behöver utföras och fördrojningen till diagnos och behandling kan också minska. Därmed kan kanske prognosen för patienterna också förbättras. Om CTU upptäcker blåstumörer i tillräckligt hög utsträckning kanske man inte behöver utföra en cystoskopi på patienter som söker för första gången med makroskopisk hematuri och som har en normal CTU-undersökning.


Blåsan kan även bedömas i uppladdningsfas (CMP och NP) och problemen med kontrastskiktning kan då undvikas. Blåstumörerna ses då som kontrastmedelsuppladdande förändringar mot den icke kontrastmedelstillblandade urinen, Figur 27. Bedömning av blåsan i uppladdningsfas kräver dock att det sker en kontrastmedelsuppladdning i blåsan och att blåsan är utspänd med icke kontrastmedelstillblandad urin.

Figur 25.
De vanligaste kontrastmedelsfaserna vid CTU: UE (A), CMP (B), NP (C) och EP (D). Vänster njure.

Figur 26.
Bedömning av blåsan i EP. Tumörerna (pil) ses som kontrastursparningar (A). Skiktning mellan kontrastmedelstillblandad urin och icke kontrastmedelstillblandad urin (B).
Syftet med den här avhandlingen var att ta reda på hur många blåstumörer som upptäcks i Uppsala med CTU jämfört med flexibel cystoskopi, i vilken fas som blåstumörerna visar högst kontrastmedelsuppladdning, i vilken fas flest blåstumörer upptäcks och hur man kan få blåsan väl utspänd. Detta för att utvärdera och optimera CTU-protokollet för att upptäcka blåstumörer.


Arbete I

Resultatet av CTU respektive flexibel cystoskopi jämfördes med patienternas diagnos. Av 435 patienter hade 55 blåscancer. CTU upptäckte 48 tumörer (87%), liksom flexibel cystoskopi. Retrospektivt ses ytterligare fyra tumörer med CTU och totalt kan 52 av 55 tumörer (95%) ses med CTU, lika många som upptäcktes med CTU och flexibel cystoskopi kombinerat primärt.

CTU enligt Uppsalas protokoll kan användas som en första undersökning vid utredning av makroskopisk hematuri för att guida patienter med blåstumörer direkt till stel cystoskopi med möjlighet att utföra TUR-B. I detta material skulle antalet undersökningar med flexibel cystoskopi minska med 12%.

Vårt resultat talar också för att patienter som söker för makroskopisk hematuri för första gången och har en normal CTU-undersökning inte nödvändigtvis behöver genomgå en cystoskopundersökning om CTU-protokollet är anpassat för att bedöma blåsan och det går att göra en adekvat bedömning av blåsan.
Arbete II

Arbete III
Alla kontrastfaser (CMP, NP och EP) hos 106, totalt 318 faser, randomiserades till en granskningsordning. Faserna granskades en och en i samma ordning av två uroradiologer. Granskarna angav i ett protokoll om det fanns blåstumör eller inte. Om det fanns blåstumör angavs antal och lokalisation för att man i efterhand skulle kunna kontrollera att det verkligen var blåstumören man angett som tumör och inte något annat fynd. I CMP upptäcktes flest tumörer. Sensitivitet och negative predictive value (NPV) var högst i CMP, 0,95 respektive 0,99.

CMP ska användas som uppladdningsfas vid CTU för att så många blåstumörer som möjligt ska upptäckas.

Arbete IV
Fyra förberedelseprotokoll för att erhålla blåsutfyllnad utvärderades:

<table>
<thead>
<tr>
<th>Vätskeintag</th>
<th>Restriktioner kissa</th>
<th>Urindrivande</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 500 ml under 1 h före CTU</td>
<td>Kissa 1 h före, ej efter det</td>
<td></td>
</tr>
<tr>
<td>2 500 ml under 1 h före CTU</td>
<td>Kissa 1 h före, ej efter det 10 mg iv</td>
<td></td>
</tr>
<tr>
<td>3 1000 ml under 2 h före CTU</td>
<td>Kissa 2 h före, ej efter det</td>
<td></td>
</tr>
<tr>
<td>4 1000 ml under 2 h före CTU</td>
<td>Kissa 1 h före, ej efter det</td>
<td></td>
</tr>
</tbody>
</table>

Instruktionerna angående vätskeintag och restriktioner om att kissa skickades hem till patienterna och alla förberedelser gjordes innan patienten kom till sjukhuset för att genomgå CTU-undersökningen.

Patienterna fick svara på hur de hade kunnat följa instruktionerna samt hur kissnödiga de kände sig både under undersökningen och upp till 24 timmar efter undersökningen. Blåsans volym hos alla patienter beräknades.
Det var lägst antal patienter som kunde följa instruktionerna i grupp 4. Patienterna i grupp 2 var mest kissnödiga både under och efter undersökningen. Patienterna i grupp 1 hade lägst blåsvolym.

Protokoll 3, där patienterna dricker 1000 ml under två timmar före undersökningen och kisser två timmar före undersökningen men inte därefter, var inte svårast att följa, påverkade inte patienterna för mycket och gav tillräckligt utspänd blåsa.

**Konklusion**

CTU inkluderande UE, CMP och EP kan användas som första undersökning vid makroskopisk hematuri för att guida patienter med blästuňörer direkt till stel cystoskopi med möjlighet till TUR-B. Patienterna bör dricka 1000 ml vätska under två timmar före undersökningen och kissa två timmar före undersökningen men inte därefter för att erhålla en utspänd blåsa.

Om CTU-protokollet är anpassat för att bedöma bläsan och en tillförlitlig bedömning kan göras, kan man överväga att inte utföra cystoskopi på patienter med makroskopisk hematuri som söker för första gången och har en normal CTU-undersökning.

**Kommentar**

CTU ska inte användas som en avancerad urograﬁ där man letar efter tumörer i njurbäcken, uretärer och bläsan som urspanningar i det utsöndrade kontrastmedlet i utsöndringsfasen.

Det är i stället dags att börja utnyttja fördelarna med CTU maximalt genom att anpassa protokollet för att upptäcka tumörer som kontrastmedelsuppladdande förändringar i hela urinvägarna, inklusive bläsan.
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