Comparison of quality of urinary bladder filling in CT urography with different doses of furosemide in the work-up of patients with macroscopic hematuria

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Abstract

Introduction: The protocol for preparation of computed tomography urography (CTU) examinations at our hospital was changed in 2013 to improve the quality of urinary bladder filling in the excretory phase. The aim of this study was to evaluate the quality of urinary bladder filling on CTU after different doses of furosemide were administered to patients with macroscopic hematuria.

Methods: The cohort was 215 patients who underwent elective CTU due to macroscopic hematuria between 2014 and 2018. 5 mg furosemide were administrated to 100 patients, 2.5 mg to 100 patients and 0 mg to 15 patients. Contrast medium layered bladders were excluded, leaving 193 patients: 92, 89 and 12 in each group. Urinary bladder volume was calculated in corticomedullary (CMP) and excretory phase (EP). Bladder distension was classified as satisfactory or not. Attenuation of bladder content in EP was noted.

Results: Average volume in EP was 370 ± 224 ml (28 e 1052) after 5 mg furosemide, 274 ± 120 ml (43 e 628) after 2.5 mg and 180 ± 104 ml (53 e 351) after 0 mg. 85% of the bladders were satisfactory distended after 5 mg, 80% after 2.5 mg and 58% after 0 mg. Average attenuation was 266 ± 89 HU (103 e 524) after 5 mg, 362 ± 156 HU (118 e 948) after 2.5 mg and 761 ± 331 HU (347 e 1206) after 0 mg. The differences in volume and attenuation were significant.

Conclusion: 5 mg furosemide is preferred rather than 2.5 mg in preparation for CTU examinations of patients with macroscopic hematuria. There was no difference between the doses concerning rate of satisfactory bladder distension, but the higher dose resulted in larger bladder volume and more suitable attenuation of bladder content.

Implications for practice: Development of CTU-image quality could improve bladder cancer diagnostics.
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Introduction

Macroscopic hematuria correlates to malignancy in the urinary tract in 24–28% of patients.1,2 Urothelial carcinoma represents the vast majority and 90–95% of those are bladder tumors.3

Bladder cancer is the fourth most common cancer amongst men in the European Union. The estimated new cases in 2015 for both sexes were around 131 000 and the deaths nearly 43 000.4 The survival prognosis is better the lower the stage and the grade of the cancer.5,6 This is why malignancy in the urinary tract follows a standardized care pathway in Sweden since 2015, meaning that symptoms raising suspicion of malignancy must be quickly assessed. Patients older than 50 years with at least one episode of macroscopic hematuria or patients with a suspicious finding during another investigation should have a urology appointment with cystoscopy investigation within 6 days from the first referral. A CT urography (CTU) examination with its report should be available at this appointment.7

A CTU is an examination of the urinary tract that includes intravenous contrast medium and an excretory phase (EP).8 It is excellent for detecting bladder cancers, which appear as...
asymmetric bladder wall thickenings.\textsuperscript{9} The bladder is best examined when adequately full, reaching around 200–500 ml when the bladder wall becomes thin and wall thickenings more prominent.\textsuperscript{10} The corticomedullary phase (CMP) has the highest sensitivity for bladder cancer detection (95%) and the highest negative predictive value (99%).\textsuperscript{11} Tumors with high vascularity are contrast enhancing in CMP and detected as filling defects in EP (Fig. 1).\textsuperscript{12} Hence, to safely ensure there is no cancer, the bladder needs to be well distended in both CMP and EP.

There are two additional requirements in the EP. Firstly, a low difference of attenuation between contrast-enhanced urine and surrounding tissues is desirable; otherwise small tumors maybe hidden by the contrast blooming effect.\textsuperscript{13} Secondly, urine with contrast medium does not easily mix with normal urine, so if the patient does not empty his bladder before the EP, the bladder will be layered with contrast-enhanced urine posteriorly and non-enhanced urine anteriorly (Fig. 2) thus hiding anteriorly located tumors.\textsuperscript{8,14}

The protocol for preparation of CTU at Uppsala University hospital (Fig. 3) was changed in 2013 to improve quality of bladder filling in the EP.\textsuperscript{15} Changes were addition of a furosemide injection at the beginning of the examination, emptying of bladder after the CMP and obtaining the EP after a 30 min delay. An earlier study concluded 10 mg of furosemide provides discomfort for patients, with urge to void and increased diuresis several hours after the examination,\textsuperscript{16} therefore 5 mg of furosemide are used today.\textsuperscript{15} However, to our knowledge, no earlier study has compared quality of urinary bladder imaging on CTU with different furosemide doses.

The aim was to evaluate the quality of urinary bladder filling on CTU after different doses of furosemide were administrated to patients with macroscopic hematuria.

**Methods**

The Regional ethical review board approved the study (2007:278). Written informed consent was obtained from all participants.

The cohort was 215 patients, randomly selected between June 1, 2014 and March 31, 2018. They all underwent elective CTU due to macroscopic hematuria. 5 mg furosemide were administrated to the first 100 patients and 2.5 mg to the next 100. The last 15 patients composed a control group and were not given any furosemide. To participate, all patients were obliged to have an eGFR above 45 mL/min/1.73 m\textsuperscript{2}. Patients on cardiovascular medication were not excluded from participation.

The CTU examinations were performed on a Siemens Definition Flash (Siemens Medical Solutions, Forchheim, Germany) according to the protocol of Uppsala University Hospital (Fig. 3). Three phases were included: unenhanced (UE), corticomedullary (CMP) and excretory phase (EP). Patients older than 50 years were also examined with a nephrographic phase (NP) before EP. To ensure a well-distended bladder in the CMP all patients were asked to...
empty their bladder 2 h prior to the examination and then drink 1 L of water divided into portions during the 2-h period. The furosemide dose was administrated intravenously approximately 5 min of water divided into portions during the 2-h period. The furosemide dose was administrated intravenously approximately 5 min before start of the first acquisition. After the UE, 60–80 ml iohexol (350 mg I/ml, Omnipaque, GE Healthcare AS, Oslo, Norway), depending on patient’s body size, was administrated at a rate of 4 ml/s with a power injector (Stellant D, Medrad Inc, Indiana, PA, USA). The bladder was emptied after the CMP or NP and the EP was performed after 30 min of waiting to ensure a well-distended bladder with contrast-enhanced urine. The CMP was scanned with DualEnergy, 100/80 kV, automatic tube current modulation (Care Dose 4D), with a quality reference of 85 mAs on tube A (automatically giving 66 mAs on tube B). The CMP had rotation time 0.33 s, collimation 64 × 0.6 mm and pitch 0.55 mm. Bolus Tracking was used with trigger level of 200 HU in descending aorta. The UE, NP and EP were scanned with single source automatic tube current modulation (CARE Dose 4D). Quality reference was 40 mAs in the UE, 95 mAs in the NP and 55 mAs in the EP and Care kV with a reference of 120 kV, slider at position 7. The UE, NP and EP all had rotation time 0.5 s, collimation 128 × 0.6 mm and pitch 0.6 mm. Axial and coronal reconstructions were performed in all phases. Slice thickness and increment was 3 mm/2.5 mm in the axial plane and 5 mm/5 mm in the coronal plane. Kernel I31 with ADMIRE, 2/2.5 mm and pitch 0.6 mm. Bolus Tracking was used with trigger level of 200 HU in descending aorta. The UE, NP and EP were scanned with single source automatic tube current modulation (CARE Dose 4D). Quality reference was 40 mAs in the UE, 95 mAs in the NP and 55 mAs in the EP. The attenuation was examined in the axial plane both visually and with three ROIs of 1 cm²: one anterior, one central and one posterior. Contrast medium layered bladders had a considerably lower attenuation anteriorly (Fig. 2). They were excluded from the study since the residual urine, not contrast-enhanced, could have contributed to falsely high volumes. The attenuation of the central ROI was compared between the groups. Patients with another tube voltage than 100 kV were excluded from the attenuation calculations, since attenuations from CT examinations with different tube voltage are not comparable.

### Statistical analysis

p-values were calculated using Student’s t-test, Pearson’s Chi-square test and 2-proportion Z-test. Significant results were considered as p-value <0.05. Volume diagrams were created with R software (version 3.3.3).^1^

### Results

22 patients were excluded due to contrast medium layered bladders, leaving 193 patients: 58 women and 135 men with an average ± SD age of 66 ± 12 years (range: 19–87 years), 5 mg of furosemide were administrated to 92 patients (23 women and 69 men, age 64 ± 13 years (19–87)), 2.5 mg to 89 patients (33 women and 56 men, age 66 ± 11 years (36–87)) and 0 mg to 12 patients (2 women and 10 men, age 69 ± 10 years (43–81)).

| Time difference | Corticomedullary phase (CMP) | Excretory phase (EP) |
|-----------------|-----------------------------|---------------------|
| Satisfactory distension of the bladder | Satisfactory distension of the bladder |
| Bladder volume (ml) | Bladder volume (ml) |
| Evaluation limits of attenuation (HU) | Evaluation limits of attenuation (HU) |

### Table 1

| Base values | Age (years) | Sex (female/male) | Furosemide dose (5 mg, 2.5 mg or 0 mg) | Time difference between corticomedullary and excretory phase |
|-------------|-------------|-------------------|--------------------------------------|-------------------------------------------------------------|
| Corticomedullary phase (CMP) | Satisfactory distension of the bladder (yes/no) | Bladder volume (ml) | Evaluation limits of attenuation (HU) | Attenuation value anteriorly, centrally and posteriorly (HU) |
| Excretory phase (EP) | Satisfactory distension of the bladder (yes/no) | Bladder volume (ml) | Evaluation limits of attenuation (HU) | Contrast medium layered (yes/no) |

The bladder distension in CMP and EP was evaluated visually from the CT-images. Bladders with primarily convex walls in both axial and coronal planes were considered satisfactory distended, whereas bladders with primarily concave walls were considered unsatisfactory distended.

The bladder volume was calculated in CMP and EP using the application “CT Volume”. The limits of the bladder content were manually marked with the free-hand ROI (Region of Interest) tool in the axial plane. Diverticula were included if present. The computer calculated the bladder volume based upon the area marked, including pixels being within the evaluation limit of attenuation only. Evaluation limits were set to −40 to 80 HU in CMP but varied when needed to include as much bladder content as possible. Variation was needed in 15 cases (6.8%), for example when artefacts due to hip prosthesis occurred (5 patients; 2.3%). The evaluation limits in EP showed greater variation since the contrast medium concentration differed between patients. The lower limit was with few exceptions −40 HU (213 patients, 99%). Two cases were at −1000 and −300 HU due to artefacts. To find the most suitable upper limit, the maximal attenuation within a 1 cm² ROI was used as a guideline. The upper limit varied from 200 to 2300 HU. The attenuation was examined in the axial plane both visually and with three ROIs of 1 cm²: one anterior, one central and one posterior. Contrast medium layered bladders had a considerably lower attenuation anteriorly (Fig. 2). They were excluded from the study since the residual urine, not contrast-enhanced, could have contributed to falsely high volumes. The attenuation of the central ROI was compared between the groups. Patients with another tube voltage than 100 kV were excluded from the attenuation calculations, since attenuations from CT examinations with different tube voltage are not comparable.

While there was some variation statistically there was no difference in time between the start of CMP and EP (p-values 0.36–0.45) (Table 2).
Bladder distension

70 (76%) bladders were satisfactory distended in CMP and 78 (85%) in EP at 5 mg. The corresponding numbers were 58 (65%) and 71 (80%) at 2.5 mg plus 7 (58%) and 7 (58%) at 0 mg (Fig. 4). Significant differences were between 5 mg and 0 mg in EP (p < 0.05) and between CMP and EP at 2.5 mg (p < 0.05). At all doses, the majority of satisfactory distended bladders in CMP were satisfactory in EP too (Fig. 5). Notably, more patients went from satisfactory in CMP to unsatisfactory in EP at 0 mg (17%) than the other groups (8%) and more patients went from unsatisfactory to satisfactory at 2.5 mg (23%) than at 5 mg (16%).

Bladder volume

The highest average volume in EP was at 5 mg and the lowest at 0 mg (Table 2). The significant differences of volumes were solely in EP between 5 mg and 2.5 mg (p < 0.001), between 5 mg and 0 mg (p < 0.001) and between 2.5 mg and 0 mg (p < 0.05).

The volume distribution was similar in CMP at 5 mg and 2.5 mg (Fig. 6). The appearance of EP differed with more patients at higher volumes and larger deviations at 5 mg. The unsatisfactory distended bladders corresponded to the lower volumes in all groups. However, there were both satisfactory and unsatisfactory distended bladders in the same volume interval.

Attenuation

7 patients were excluded from the attenuation calculations since their examinations were performed with another tube voltage than 100 kV. This reduced the cohort to 186 patients; 56 women and 130 men, 91 patients were given 5 mg furosemide, 83 patients 2.5 mg and 12 patients 0 mg. The average attenuation at 5 mg was lower than at 2.5 mg (p < 0.001) and at 0 mg (p < 0.001). The average attenuation at 2.5 mg was lower than at 0 mg (p < 0.001) (Table 2).

Discussion

The results showed that 5 mg of furosemide provide a larger average bladder volume in EP than 2.5 mg and 0 mg. The small difference in furosemide dose provide a significant difference in bladder volume. The time difference was not an influencing factor. Concerning CMP, there was no surprise no significant difference of volume was found. The effect of furosemide comes approximately 10 min after administration according to the manufacturer, hence should not impact bladder filling in the CMP. The control group had the lowest average volume and the lowest ratio of satisfactory distension. However, this group consisted of 12 patients and was not classified as large enough to draw any conclusions, hence will not be analyzed further.

As mentioned in the introduction, when evaluating the bladder, the distension is more important than the size. Could the lower volume at 2.5 mg be enough for evaluation? It is difficult to set a volume satisfactory for evaluation. The lower volumes have been categorized as unsatisfactory distended in some patients and satisfactory in others. Patients being individuals with different bladder capacity could explain this phenomenon; a volume giving a convex bladder in one person could result in a concave in another. It is however clear that there is a higher chance of satisfactory distension the larger the volume. The difference concerning satisfactory distension in EP between 5 mg and 2.5 mg was not significant, indicating the dose could be lowered to 2.5 mg without risking poorer quality of bladder

Table 2

| Furosemide | Volume (ml) Corticomedullary phase | Volume (ml) Excretory phase | Attenuation (HU) | Time difference (minutes) |
|------------|-----------------------------------|-----------------------------|-----------------|-------------------------|
| 5 mg       | 327 ± 224 (28–1052)               | 370 ± 189 (41–895)          | 266 ± 89 (103–524) | 31 ± 8 (15–62)          |
| 2.5 mg     | 271 ± 191 (23–877)                | 274 ± 120 (43–628)          | 362 ± 156 (118–948) | 32 ± 7 (21–61)          |
| 0 mg       | 265 ± 295 (32–946)                | 180 ± 104 (53–351)          | 761 ± 331 (347–1206) | 34 ± 11 (22–61)         |

Figure 4. Ratio of distension in each group and phase.
filling. However, before conclusions can be drawn, another important aspect must be considered. As mentioned in the introduction, proper evaluation of the EP images not only requires a well-distended bladder, but the attenuation of the contrast-enhanced urine is also of importance. Considering that the attenuation of a bladder tumor usually is around 57 HU in EP\textsuperscript{12}, the lower attenuation at 5 mg is more suitable for evaluation of the bladder.

Possible limitations of the study are:

1. The patient test groups were limited, and the control group was unfortunately particularly small. Initially the idea was to have a larger control group, but as data was collected it became obvious the quality of bladder filling was poor with low volume, unsatisfactory distension and high attenuation in EP. Therefore, it was unethical to continue with 0 mg furosemide. It is however important to remember that these patients had regular quality of bladder filling in CMP and that cystoscopy was performed according to routine. A larger study population would probably result in more reliable statistics. Nevertheless, significant results were found.
2. The setting of the study was not randomized. Medical staff knew in advance which dose of furosemide was administrated. Theoretically there could have been a placebo effect, but it is unlikely as the kidneys are autonomously innervated organs and therefore difficult to influence by will.
3. Only one person acquired all the data, hence no comparison of intra- or interobserver variability was made. However, the risk of misjudgment was minimized by supervision of a uroradiology specialist.
4. There were only two categories of distension, meaning those bladders not being strictly concave or convex might have been categorized inadequately. This may explain why there was a significant difference of satisfactory distension between CMP
and EP at 2.5 mg whereas the average volume was similar. Addition of a third category might have given results closer to reality, however more complicated to draw conclusions from. The categories chosen were easy to define and to compare.

5. The evaluation limits were changed from time to time to include as much bladder content as possible in the volume calculation. A standard limit is preferable at a first glance, but it was impossible to find one suitable for all patients since the urine contrast medium concentration differed and some examinations had artefacts. Changing the evaluation limit was important to ensure quality of the results.

Aside from the limitations mentioned above, there is one more important aspect. To evaluate which dose of furosemide is the most optimal, both quality of bladder filling and patient experience is important. Logically, with larger bladder volume the higher the risk patients experience problems or discomfort during and after the examination. Further research assessing patients' experiences with these furosemide doses needs to be done for proper evaluation of the effect of furosemide in the CTU protocol.

Conclusion

In conclusion, 5 mg furosemide is preferred rather than 2.5 mg in preparation for CTU examinations of patients with macroscopic hematuria. There was no difference between the doses concerning rate of satisfactory bladder distension, but the higher dose resulted in larger bladder volume and more suitable attenuation of bladder content.

Conflict of interest statement

None declared.

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