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Comparison of Conventional and Triple Bolus Computed Tomography Urography Protocols for Radiation Dose Reduction in Hematuria Evaluation: A Randomized Controlled Trial

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Runninghead: Triple Bolus CT for Hematuria Evaluation

Keywords: hematuria, computed tomography, radiation, urologic neoplasms,

ABSTRACT

Purpose: Computed tomography urography is the diagnostic tool of choice for evaluating hematuria. In keeping with the ALARA (as low as reasonably achievable) principle, we evaluated a triple bolus computed tomography (TBCT) protocol designed to reduce radiation exposure.

Materials & Methods: Patients with macroscopic or microscopic hematuria were prospectively randomized to conventional CT (CCT) (n=100) or TBCT (n=100). The TBCT protocol entails two scans: pre-contrast scan followed by three contrast injections at 40 seconds, 60 seconds, and 20 minutes prior to the second scan to capture all three phases. The CCT protocol requires four scans: pre-contrast scan, and three post-contrast scans at the corticomedullary, nephrographic, and excretory phases. Radiation exposure and the detection of urologic pathology were recorded based on radiology reports.

Results: There were no differences in patient demographics or BMI between the two groups. TBCT exposed patients to 33% less radiation (1715 vs. 1145 mGy*cm, $p<0.001$ for CCT and TBCT, respectively). For macroscopic hematuria, the pathology detection rates were 70% for TBCT and 73% for CCT ($p=0.72$). For microscopic hematuria, the detection rates were 59% for TBCT and 50% for CCT ($p=0.68$). In both groups, the rates of detection of urolithiasis, renal

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cysts, urological masses, bladder pathology, and prostate pathology were no different between TBCT and CCT.

Conclusion: In both the setting of macroscopic and microscopic hematuria evaluation, triple bolus CT significantly reduces radiation exposure while providing equivalent detection of genitourinary pathology compared to conventional CT. The ability to detect upper tract filling defects was not specifically tested.

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Introduction

Over 75 million CT scans are performed yearly in the United States[1]. Associated radiation exposure accounts for an estimated 1.5-2% of all cancers nationally, likely attributable to DNA damage[2]. Based on the current stochastic, "no-threshold" model, efforts to reduce radiation exposure are conducted as part of the ALARA (As Low As Reasonably Achievable) principle[3].

Each year, over 400,000 patients in the United States undergo urinalysis for various indications; 13% demonstrate microscopic hematuria[4-7]. Hematuria evaluation often requires exposure to high doses of ionizing radiation, as most guidelines recommend performing CT urography due to its high sensitivity and specificity for detecting urinary tract pathology[8,9]. Accordingly, CT urography in the evaluation of hematuria results in an estimated 575 (0.6%) radiation-induced cancers per 100,000 patients[10]. Conventional CT urography (CCT) requires four scans: a pre-contrast scan, a delayed post-contrast phase, an arterial phase and a venous phase. Triple bolus CT urography (TBCT), introduced by Kekelidze et al in 2010[11], involves two scans: a pre-contrast and a post-contrast scan after three individual boluses of contrast spaced over time.

In this randomized, controlled, non-inferiority trial, we hypothesized that among patients with hematuria, TBCT would detect pathology at an equal rate as CCT. A secondary hypothesis is that TBCT would expose patients to less radiation than CCT.

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Materials and Methods

After obtaining Institutional Review Board approval, from August 2016 to March 2020, at the University of California – Irvine, we enrolled patients >18 years of age with hematuria for whom CT urography had been ordered. Exclusion criteria were prior adverse reaction to iodine or intravenous (IV) contrast, acute kidney injury, estimated glomerular filtration rate (eGFR) <40 mL/min, or pregnancy. Participant entry is outlined in Figure 1.

After providing informed consent, patients underwent computer-generated simple randomization to either TBCT urography or CCT urography. We recorded patient demographics, change in creatinine values, and pathology detected based on the radiology report. The abbreviated MDRD equation was used to calculate eGFR values before and after the CT scan. All CT scans were read by faculty radiologists unblinded to the type of protocol used. Dose-length product (DLP) as a measure of radiation exposure was recorded. The cohort was analyzed by macroscopic versus microscopic hematuria. The primary outcome of the study was detection of pathology and the secondary outcome was radiation exposure.

Triple Bolus CT Urography Protocol

Patients are fasted for three hours prior to the study, except for 32 ounces of water given 90 minutes prior. A pre-contrast helical scan is followed by three temporally spaced contrast injections at 40 seconds, 60 seconds and 20 minutes prior to a post-contrast helical scan. The initial bolus of IV contrast is delivered at 2 mL/s. After 20 minutes, the second bolus is administered at 1.5 mL/s. After 60 seconds, the third bolus of IV contrast is given at 3 mL/s. Following a 40-second delay, the post-contrast scan is performed (Figure 2A). The total amount

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of contrast administered ranged from 100-150 mL depending on the patient's weight, and was divided into three boluses.

Conventional CT Urography Protocol

Patients are fasted for three hours prior to the study, except for 32 ounces of water given 90 minutes prior. A pre-contrast helical scan is performed, followed by a 100 mL injection of contrast at 2 mL/s; three post-contrast helical scans are obtained at 40-seconds (corticomedullary phase), 100-seconds (nephrographic phase), and 15-minutes (urographic phase) (Figure 2B).

Image Quality Assessment

Three reviewers, including two faculty radiologists and one faculty urologist, performed a standard, non-validated, image quality assessment for the CT scans. Each reviewer rated the CT scans from 1 to 5 (1= poor; 5=excellent) in nine categories: differentiation between renal cortex and medulla, opacification of veins, arteries, collecting system, and ureters, and image quality of veins, arteries, renal parenchyma, and collecting system for a total possible score of 45 (Figure 3).

Statistical Analysis

A power analysis determined that 100 patients per group would be sufficient to detect a non-inferiority margin of 10% between TBCT and CCT with a power of 0.9 based on detection of urologic pathology. Categorical variables were compared using chi-square test. The mean image quality assessment scores of CT scans obtained using the same scanner, and mean DLP were

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compared using unpaired Student's t-test. P-values less than 0.05 were deemed statistically significant. Statistical tests were performed using Microsoft Excel 2019 (Microsoft, Redmond, WA, USA).

Results

Patient Population

Two-hundred patients were randomized to either TBCT (n=100) or CCT (n=100) (Table 1). The study population included 119 males (60%), with a mean age of 63.6 years (range: 21-96 years), and 81 females (40%), with a mean age of 56.6 years (range: 25-82 years). There were no differences in sex, age, ethnicity, BMI, pre-scan eGFR, or type of CT scanner used between the groups. There was no difference in the hospital charge for the two protocols, as billing and collection amounts are not influenced by the CT protocol utilized.

One-hundred twenty-nine patients had macroscopic hematuria. This group consisted of 81 males (63%) and 48 females (37%), with an average age of 61.4 years (range: 21-96 years). Sixty-six of these patients had CCT (51%) and 63 patients had TBCT (49%). Compared to CCT, the TBCT scans were performed significantly more with the less advanced Siemens Sensation 16-slice scanner (p=0.04) than with the Philips iCT 128-slice scanner (p=0.01). There were no differences in sex, age, BMI, ethnicity, or number of patients who underwent cystoscopy prior to their CT scan.

Seventy-one patients had microscopic hematuria. Thirty-eight of these patients were male (53%) and 33 patients were female (47%). The average age was 59.5 years (range: 25-88 years). Thirty-

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four patients had CCT (48%), and 37 patients had TBCT (52%). There were no differences in sex, age, BMI, ethnicity, the type of scanner, or number of patients who underwent cystoscopy prior to their CT scan.

Radiation Exposure

Overall, the DLP of the TBCT group was significantly lower than that of the CCT group (1144 vs. 1714 mGy*cm, respectively; $p<0.001$), representing a 33% reduction in radiation exposure. This finding was consistent in both the macroscopic hematuria patients, (DLP = 1221 vs. 1752 mGy*cm, $p<0.001$) and the microscopic hematuria group (DLP = 1016 vs. 1640 mGy*cm, $p<0.001$).

Pathology Detection Rates

In patients with macroscopic hematuria, pathology was detected in 53 CCT scans (80%) and 48 TBCT scans (76%) ($p=0.72$). There were no significant differences in rates of detection of urological masses, urolithiasis, renal cysts, bladder pathology, prostate pathology, or non-urological pathology between CCT and TBCT **(Table 2)**. Urological neoplasms were detected in 7 CCT scans (11%) and 8 TBCT scans (13%). The masses detected on CCT included 5 bladder tumors (average size = 5.0 cm) and 2 kidney tumors (average size = 1.1 cm); on TBCT the masses detected were 2 bladder tumors (average size = 2.0 cm), 5 kidney tumors (average size = 2.6 cm), and 1 prostate nodule (4.6 cm). All patients with a urological tumor were over 50 years of age.

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In patients with microscopic hematuria, pathology was detected in 19 CCT scans (56%) and 23 TBCT scans (62%) (p=0.42). No differences were found between TBCT and CCT in rates of detection of urological neoplasms, urolithiasis, renal cysts, bladder pathology, prostate pathology, or non-urological pathology **(Table 2)**. Urological neoplasms were detected in 1 CCT scan (3%), a 1.6 cm kidney tumor, and in 1 TBCT scan (3%), a 1.6 cm bladder tumor; both patients were over 50 years of age.

With regard to renal-bladder ultrasonography, there was concordance with CCT in six of 10 patients (60%) with both ultrasound and CT urography. Among patients undergoing TBCT, 7 patients had a prior ultrasound, 6 of which had concordance with TBCT (88%). With regard to urine cytology results, in the CCT group, 7 patients had atypical urothelial cells on cytology, 2 of which had a bladder tumor detected on imaging and confirmed on cystoscopy. In the 11 TBCT patients with atypical urothelial cells on cytology, 1 had a bladder tumor detected on imaging and confirmed on cystoscopy.

Out of 8 CCT patients with bladder irregularities at cystoscopy, 4 were detected on CCT (50%); pathologies missed by CCT included 3 bladder tumors and 1 case of inflammatory changes. One bladder tumor was identified in a 46-year-old male, while all other masses were in patients above 50 years of age. In comparison, 8 TBCT patients had bladder irregularities on cystoscopy, 5 of which were detected on TBCT (63%). The three pathologies missed by TBCT included 1 bladder tumor in a 53-year-old female and 2 cases of inflammatory changes.

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Effect on Kidney Function

The average amount of IV contrast administered was higher in the TBCT group (112 mL vs. 101 mL, p<0.001). There were no differences in post-scan mean creatinine (0.84 vs. 0.91 mg/dL, p=0.25) or eGFR (92.3 mL/min/1.73 m^2 vs. 85 mL/min/1.73 m^2, p=0.12); however, post-scan creatinine values were only available for 46 CCT patients and for 28 TBCT patients. In patients with a post-scan eGFR within 1 month of the CT scan, the change in eGFR was 0.35 mL/min/1.73 m^2 in CCT patients and -2.75 mL/min/1.73 m^2 in TBCT patients (p=0.55). The change in eGFR for patients with post-scan eGFR after 1 month was 4.39 mL/min/1.73 m^2 in CCT patients and -1.7 mL/min/1.73 m^2 in TBCT patients (p=0.11).

Image Quality Assessment

In the 73 CCT patients and 68 TBCT patients scanned with the Siemens 64-slice scanner, the mean total image quality score of CCT was significantly higher than TBCT (41.0 vs. 38.2, p<0.001). CCT was rated significantly higher in differentiation between renal cortex and medulla (4.6 vs. 4.1, p<0.001), intrarenal distension (4.5 vs. 4.2, p<0.001), ureteral opacification (4.2 vs. 3.9, p=0.001), renal parenchyma (4.6 vs. 4.2, p<0.001) and collecting system (4.3 vs. 4.0, p=0.002). There was no difference in the rating of venous opacification (4.7 vs. 4.6, p=0.07), arterial opacification (4.8 vs. 4.7, p=0.05), bladder distension (4.3 vs. 4.2, p=0.18), or vasculature (4.8 vs. 4.7, p=0.11).

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Discussion

Earlier this year, the American Urological Association released hematuria management guidelines that incorporate a risk stratification system[8]. Patients considered high risk are recommended CT urography in addition to cystoscopy. Renal ultrasound, or foregoing imaging with initial repeat urinalysis at 6 months is recommended for lower risk patients. The updated guidelines will reduce radiation exposure to patients at low risk of malignancy[12]. Our findings generally support the guidelines, as all but one of 21 urologic tumors were in patients over 50 years of age and detected by either cystoscopy or imaging.

TBCT markedly reduces radiation exposure, because only 2 scans are required compared to the 4 scans obtained with the CCT protocol. The consolidation of phases in TBCT resulted in a 30-38% reduction in DLP compared to the CCT protocol; this reduction in radiation is not 50% because the arterial and urographic phases of CCT only scan a portion of the abdomen and pelvis. Notably, the consolidation of phases did not hinder the diagnostic quality of the CT scan among patients with either microscopic or macroscopic hematuria, as there were no significant differences in rates of detection of urologic pathology between TBCT and CCT. TBCT appears to be safe, as, despite the additional 12 ml of contrast material, there was no significant difference in impact on kidney function compared to CCT. Based on statements from the American College of Radiology, a dose-toxicity relationship between contrast and contrast-induced nephropathy has not been identified at diagnostic doses[13]. Of note, unlike studies performed on CT scanners designated for research-use only, our findings were obtained on scanners used in daily clinical care and thus are relevant to standard clinical practice.

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Our findings regarding radiation are consistent with a retrospective review by Abedi and colleagues evaluating TBCT in patients with renal cortical neoplasms[14]. In this series, the DLP was 40% lower in the TBCT group. While limited data suggest an amount of absolute reduction in radiation that would be clinically significant, based on the ALARA principle, lower radiation is always better provided there is no compromise in patient evaluation.

In the absence of a consensus, myriad CT urography protocols have been proposed[15]. One heavily investigated protocol as a dose-reduction measure is the split-bolus CT urography, which involves a combination of the nephrogenic and urographic phase after a timed injection with 2 boluses. While several retrospective reviews have determined the split-bolus protocol to provide reduced radiation exposure and adequate image quality, there are no randomized, controlled trials to confirm these findings[16-19].

One fear of combined sequence protocols is that the entirety of injected contrast is not visualized in the urinary tract as in a dedicated urographic phase in CCT. This is important for detecting upper urinary tract lesions. The split-bolus protocol, in a study by Shaish et al, is reported to have high sensitivity in detecting upper tract urothelial carcinoma, but has low positive predictive value[20]. Despite lower rated urinary tract opacification, in our study TBCT detected upper tract lesions similar to CCT, although no cases were ureteral in origin. The importance of this shortcoming may be overstated as most ureteral tumors lead to accompanying hydronephrosis that can be appreciated on CT regardless of ureteral opacification[21].

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Our study demonstrates that the ability to detect pathology by TBCT was equivalent to CCT despite statistically significantly lower image quality ratings. However, in all cases, the image quality score for TBCT was acceptable with all but one rating above 4.0 on a scale of 1.0 (poor) to 5.0 (best).

The rates of pathology detected in our study are consistent with those reported in the literature for patients with hematuria[22-25]. Our most common benign finding was renal cyst(s) ranging from 29-40% of patients. This rate of detection is consistent with the prevalence of renal cysts in the general population and thus likely not the source of either microscopic or macroscopic hematuria[26,27]. Urological tumors were detected in 11-13% of macroscopic hematuria patients and in 3% of microscopic hematuria patients, compared to 6-22% and 1-5% of macroscopic and microscopic hematuria patients, respectively, reported in other studies[22-25]. Given the reduced radiation dose and maintained ability to detect pathology, TBCT should be considered for adoption as the new standard of care in evaluation of macroscopic and microscopic hematuria.

Our study has limitations. First, only 75 of the 200 patients had post-scan creatinine data available. Secondly, the effective dose was not calculated to estimate radiation exposure. Effective dose is calculated assuming the radiated region is uniform, which is not valid in protocols using dose modulation per slice. As such, we used DLP as it represents a more accurate estimate of the patient's radiation exposure after controlling for BMI and scan length.

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Conclusions

The triple bolus CT urography protocol reduces radiation exposure up to 38% compared to conventional CT urography. Triple bolus CT urography is equivalent to conventional CT urography in detection of both general urologic pathology and renal masses. Its specific ability to detect upper tract filling defects was not tested given the rarity of this condition among patients presenting with hematuria (incidence of <1%)[22-25]. The effect of the increased dose of contrast in the triple bolus CT protocol should be further explored in future studies.

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Table 1: Baseline Characteristics for the entire cohort

Variables	CCT	TBCT	p-value
Mean age, years (range)	60.24 (21-96)	61.21 (25-82)	0.65
Gender, N (%)			0.47
Male	57 (57%)	62 (62%)	
Female	43 (43%)	38 (38%)	
Mean BMI, kg/m^2 (SD)	27.01 (4.85)	27.71 (6.17)	0.39
Creatinine, mg/dL (SD)			
Pre-scan	0.88 (0.23)	0.91 (0.19)	0.46
Post-scan	0.84 (0.21)	0.91 (0.17)	0.11
Change in creatinine	-0.05 (0.21)	0.02 (0.10)	0.09
eGFR, mL/min/1.73 m^2 (SD)			
Pre-scan	88.9 (18.8)	84.4 (18.8)	0.12
Post-scan	92.3 (20.6)	85 (18.5)	0.12
Change in eGFR	1.4 (13)	0.6 (8.5)	0.78
Charlson Comorbidity Index (range)	2.75 (0-14)	2.77 (0-10)	0.96
CT scanner type, N (%)			
Siemens Sensation 64	68 (68%)	73 (73%)	0.53
Siemens Sensation 16	3 (3%)	10 (10%)	0.04
Philips iCT SP 128	17 (17%)	9 (9%)	0.09
Philips iCT SP 256	3 (3%)	3 (3%)	1
Scanner type not available	9 (9%)	5 (5%)	0.26

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CT scan length, cm (SD)	44.9 (4.4)	45.4 (5.3)	0.54
Type of hematuria, N (%)			0.66
Macroscopic	66 (66%)	63 (63%)	
Microscopic	34 (63%)	37 (37%)	

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Table 2. Pathology detection rates for CCT and TBCT in patients with macroscopic hematuria and microscopic hematuria

Macroscopic Hematuria*			
Detection Rate, n (%)	CCT (n=66)	TBCT (n=63)	p-value
Urological Pathology	53 (80%)	48 (76%)	0.72
Urolithiasis	19 (29%)	20 (32%)	0.72
Renal Cyst	26 (39%)	23 (37%)	0.74
Urological Mass	7 (11%)	8 (13%)	0.71
Bladder Pathology	24 (36%)	17 (27%)	0.25
Prostate Pathology	16 (24%)	16 (25%)	0.43
Other Findings**	20 (30%)	18 (29%)	0.83
Microscopic Hematuria*			
Detection Rate, %	CCT (n=34)	TBCT (n=37)	p-value
Urological Pathology	19 (56%)	23 (62%)	0.35
Urolithiasis	5 (15%)	7 (19%)	0.64
Renal Cyst	10 (29%)	15 (40%)	0.33
Urological Mass	1 (3%)	1 (3%)	0.95
Bladder Pathology	8 (24%)	7 (19%)	0.63
Prostate Pathology	5 (15%)	7 (19%)	0.64
Other Findings**	4 (12%)	6 (16%)	0.23

*Total percentages exceed 100% due to several patients having more than one pathology detected on CT scan

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**Other findings included renal laceration, urethral diverticulum, horseshoe kidney, papillary necrosis, adrenal nodules, ovarian cystic lesions, small bowel inflammation, cortical bone thickening, hepatic lesions, cholelithiasis, and pulmonary nodules.

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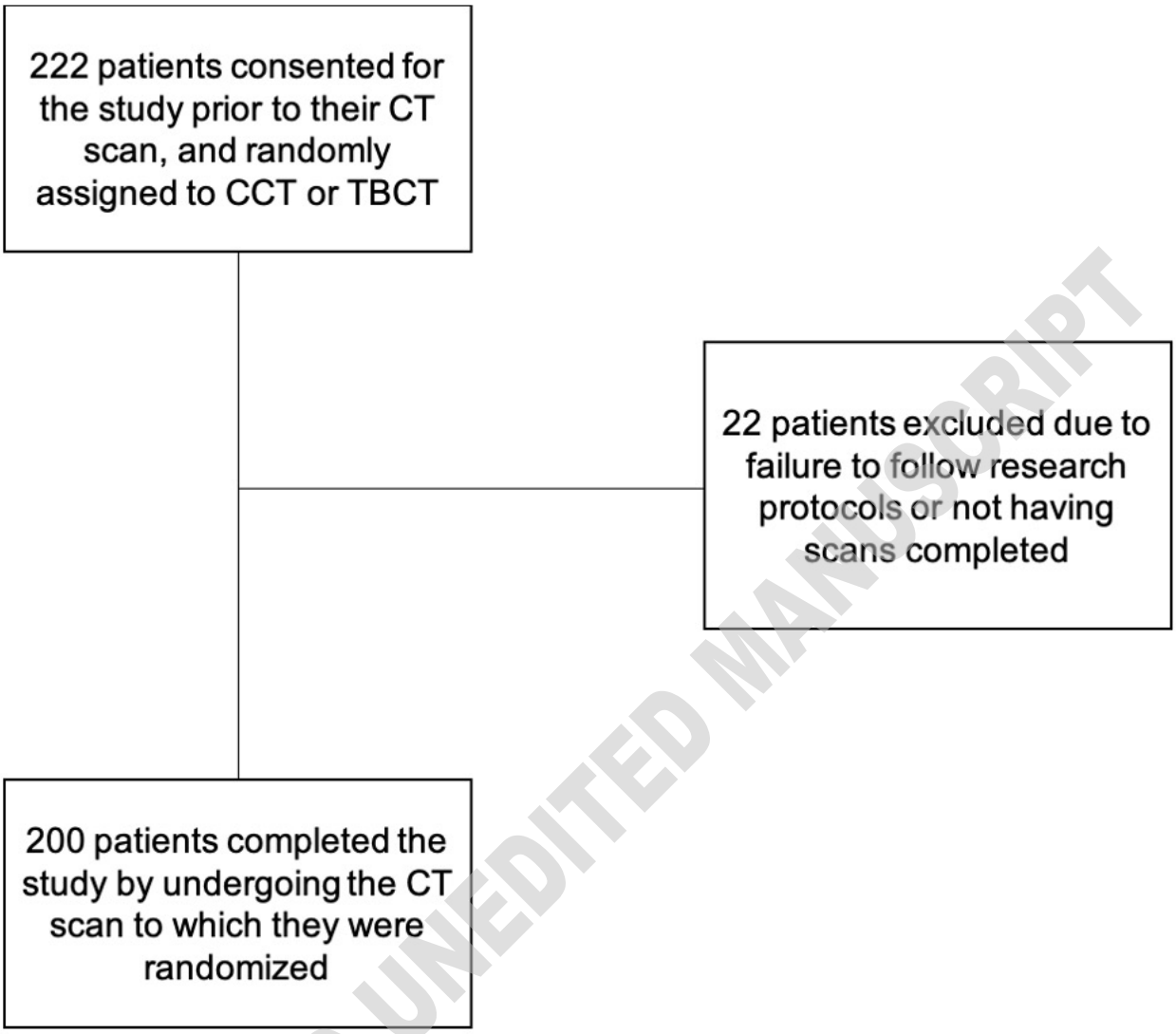

Figure 1. Flow chart of participant entry.

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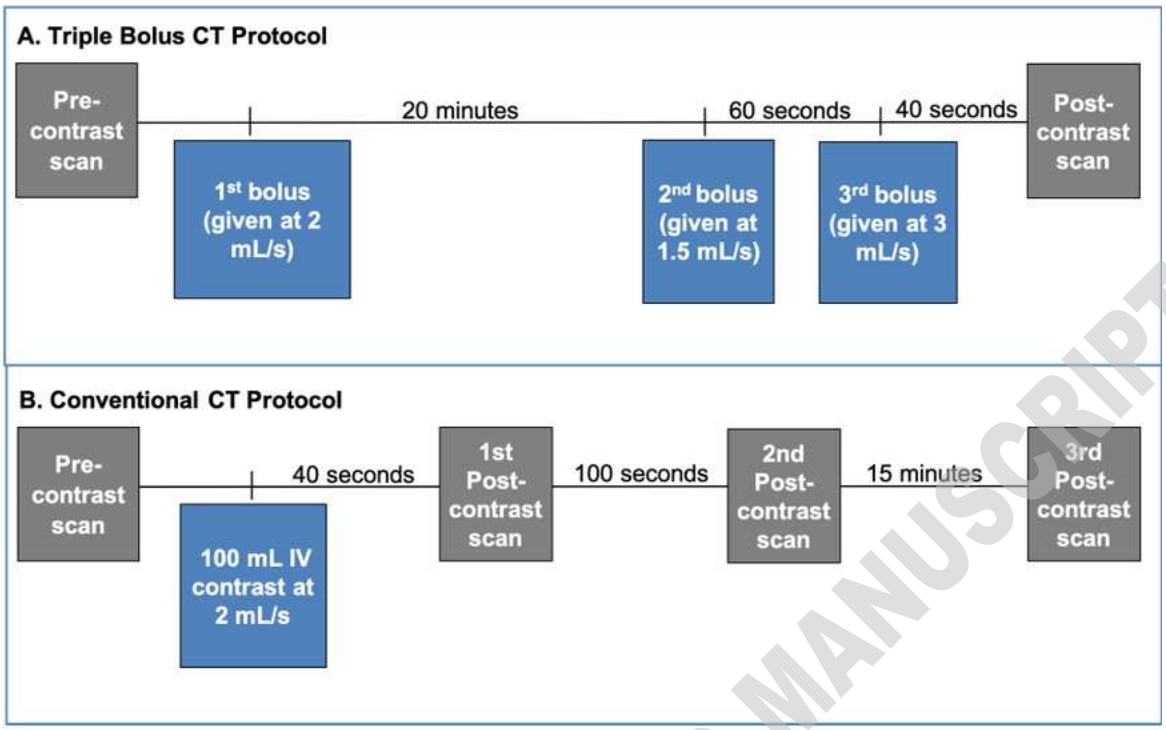

Figure 2. A) The triple bolus CT protocol consists of a pre-contrast scan, followed by 3 timed bolus injections of IV contrast, and a post-contrast scan. **B)** The conventional CT protocol consists of a pre-contrast scan, a single injection of IV contrast, followed by 3 timed scans to capture the corticomedullary, nephrogenic, and urographic phases.

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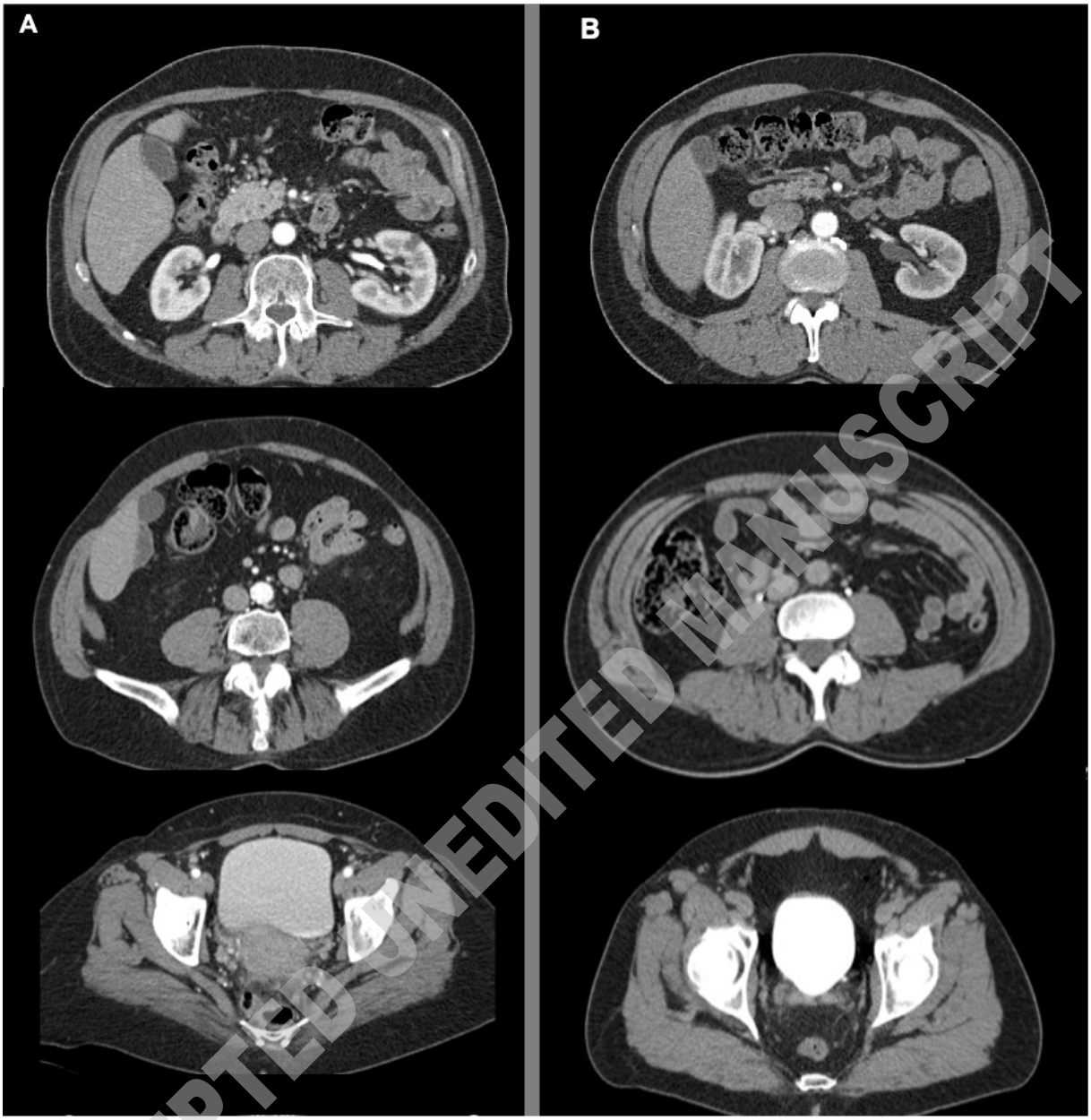

Figure 3. Sample images of CT urography from three separate scans using A) the triple bolus CT protocol (average scores of 42.3, 26.3, 40.3 in the top, middle, and bottom images) and B) the conventional CT protocol (average scores of 43.7, 44.7, 41.7 in the top, middle, and bottom images).

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