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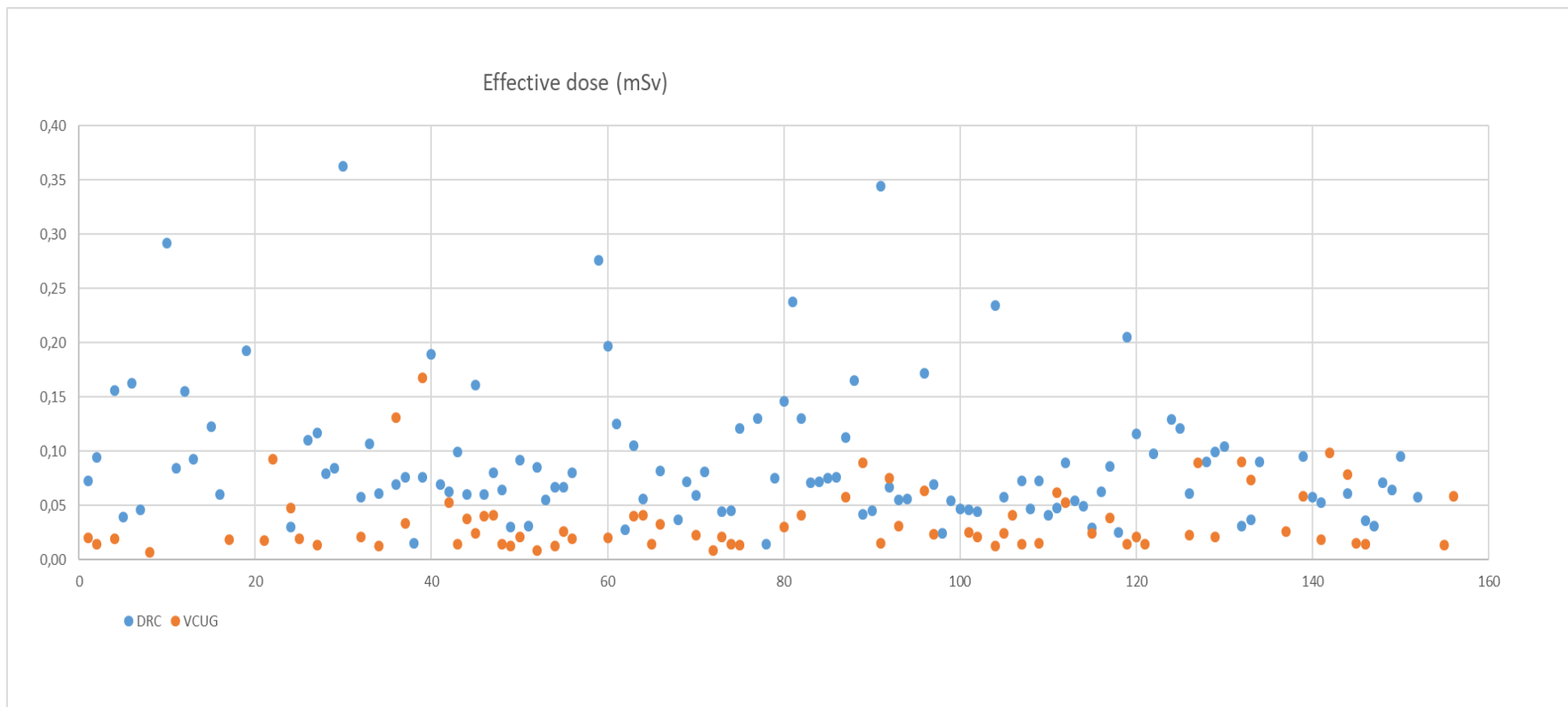
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Figure1



**RADIATION EXPOSURE IN VUR DIAGNOSTICS: A COMPARATIVE STUDY
OF DIRECT RADIONUCLIDE CYSTOGRAPHY AND VOIDING
CYSTOURETHROGRAM**

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Authors' contributions:

HRV: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing – review & editing

LR: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing – review & editing

HL: Effective dose analysis, writing, review and editing

TN: Effective dose analysis, writing, review and editing

AS: Effective dose analysis, writing, review and editing

PR: Writing, Review & Editing

MK: Statistical analysis and editing

NP: Conceptualization, Methodology, Investigation, Resources, Writing - original draft,
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All authors approved the final manuscript as submitted and agree to be accountable for
all aspects of the work.

ABSTRACT

Introduction: Voiding cystourethrography (VCUG) is the standard for diagnosing vesicoureteral reflux (VUR) but has been criticized for radiation exposure. Direct radionuclide cystography (DRC) was developed to reduce this risk. We aimed to assess DRC's efficacy as a screening tool and compare its radiation burden to VCUG.

Materials and Methods: We retrospectively analyzed patient records encompassing children who underwent VCUG or DRC to diagnose VUR from 2011 to 2020 at our hospital.

Results: 156 children were included (median age 0.75 years, 53.8% females). Indications included urinary tract infection in 71.2% of patients and antenatal hydronephrosis in 26.9%. DRC was performed on 122 patients (78.2%) and VCUG on 96 patients (61.5%), with solitary use in 38.5% and 21.8% of cases, respectively, and combined application in 39.7%. DRC detected VUR in 35.3% (43/122) and VCUG in 61.5% (59/96) of patients. Bladder filling rates differed significantly between DRC (37%) and VCUG (67%) ($p < 0.0001$).

Median radiation doses were lower in VCUG (0.023 mSv) than in DRC (0.073 mSv). For patients requiring complementary VCUG after DRC, the median radiation dose for DRC was 0.063 mSv ($p < 0.0001$), resulting in a total median dose of 0.098 mSv. Cost analysis revealed VCUG as more cost-effective, with an additional expenditure of approximately 345 euros per patient undergoing DRC in our cohort.

Conclusions: DRC imposed a higher radiation burden on patients than VCUG and often necessitated follow-up VCUG for positive cases. This challenges the utility of DRC as a low-radiation alternative in VUR screening.

Keywords: reflux; VCUG; DRC; ionizing; radiation dose

Abbreviations:

VCUG Voiding cystourethrography

VUR vesicoureteral reflux

DRC Direct radionuclide cystography

UTI urinary tract infections

RBUS renal and bladder ultrasound

EUA European Association of Urology

AUA American Urological Association

DMSA dimercapto succinic acid

PUV posterior urethral valves

DAP Dose Area Product

ARPKD Autosomal recessive polycystic kidney disease

MCKD Medullary cystic kidney disease

PACS Picture Archiving and Communication System

ED Effective dose

ceVUS contrast-enhanced voiding urosonography

Introduction

Vesicoureteral reflux (VUR) is defined as the retrograde movement of urine from the bladder into the ureter(s), due to a deficient closure mechanism at the ureterovesical junction and inefficient ureteral dynamics [1]. In children without a history of urinary tract infections (UTI), the prevalence of VUR ranges between 0.4 to 1.8%. This prevalence escalates to 16% in children with prenatal hydronephrosis and to 35% in those with febrile urinary tract infections [2–4]. Most guidelines advocate for VUR exclusion following urinary tract infections, particularly after recurrent or atypical infections [5–8].

Voiding cystourethrography (VCUG) has been the standard method of diagnosing vesicoureteral reflux [5]. While guidelines regarding the diagnosis of VUR vary across different countries, they all include VCUG at some stage of diagnosis. The European Association of Urology (EUA) advises using VCUG to diagnose VUR in infants after their first febrile UTI, in older children with non-E.coli UTIs or recurrent infections, and when abnormalities such as upper tract dilation are observed in renal and bladder ultrasound (RBUS) [5]. The British NICE guidelines suggest VCUG for infants under six months of age with atypical or recurrent UTIs, non-E.coli infections, RBUS-detected dilation, or a family history of VUR [6]. Conversely, the American Urological Association (AUA) endorses VCUG for infants with significant hydronephrosis, hydroureter, abnormal RBUS, or UTIs during observation. Yet, they emphasize that screening asymptomatic infants for VUR is optional due to limited evidence [7]. The

Urological Association of Asia advises VCUG after repeated febrile UTIs or when RBUS or DMSA scan abnormalities are present [8].

Although VCUG has proven its utility, it entails exposing the children to ionizing radiation and catheterization. Furthermore, it carries an additional risk of UTIs [9]. The radiation exposure depends upon the technique and equipment used. The effective dose estimate ranges from 0.03 to 0.3 mSv [10]. To minimize radiation exposure, direct radionuclide cystography (DRC) has been employed, offering effective doses of approximately 0.048-0.096 mSv when using the recommended activity (20-40 MBq) of technetium-99m (^{99m}Tc) [11]. DRC functions as a binary assessment tool for detecting vesicoureteral reflux. If VUR is identified, a subsequent VCUG is essential for a detailed classification of its severity [5].

Our primary objective was to evaluate the efficacy of implementing DRC as an initial screening method for vesicoureteral reflux in attempting for lower radiation doses. The secondary aim focused on quantifying the radiation doses associated with this diagnostic approach.

Materials and Methods

We retrospectively collected and analyzed patient records for all children who underwent VCUG, or DRC at Turku University Hospital, Finland, from 2011 to 2020. Inclusion criteria comprised age under 16 years, suspicion of VUR, and no prior examinations for VUR. Exclusion criteria included suspicion of posterior urethral valves (PUV) or fistula, trauma, and prior examinations for VUR.

Our hospital serves as a tertiary pediatric urology center, serving to the region of southwest Finland, which accommodates approximately 15% of the Finnish population. During the study period, our hospital favored DRC as the primary modality when VUR was suspected. When reflux was identified during DRC, a subsequent VCUG was conducted to ascertain the extent of VUR. However, if technical issues arose during DRC, such as inadequate bladder filling, a VCUG was often performed following consultation with a physician. In cases of suspected anatomical abnormalities like posterior urethral valves (PUV) or others, a VCUG was performed directly, bypassing DRC.

We collected patient data including age, sex, indications, comorbidities and urinary tract anomalies. From the examinations, we gathered information on the amount of radiation, the bladder filling volume, and the side and grade of VUR. Bladder filling volume was compared to the calculated average bladder size using Koff's formula: bladder capacity (ml) = (age in years + 2) × 30 ml [12]. Activities for DRC was reported in MBq, while

VCUG utilized the Dose Area Product (DAP). Both exposures were subsequently converted to effective doses in mSv by medical physicists.

VCUG was conducted following the hospital's standard operating procedure. The radiation dose from VCUG was evaluated using the PCXMC 2.0.1.4. Monte Carlo calculating program (Radiation and Nuclear Safety Authority, Helsinki, Finland). For this purpose, the examination specific data (DAP, kVp, mAs, the size of the radiated area and the equipment used) were collected from Philips Vue Picture Archiving and Communication System (Philips Vue PACS, Philips Healthcare, Koninklijke, Netherlands). Due to the nature of the examination, the average area used in the fluoroscopy procedure was used in dose evaluation.

DRC commenced with bladder catheterization by a trained nurse and subsequent bladder emptying. The nuclear medicine physician administered 20 MBq of ^{99m}Tc -pertechnetate through the catheter into the bladder after which the bladder was slowly filled with a saline. Filling volumes ranged between 7 – 300 ml (10-119% of calculated average bladder size), with a mean volume of 65 ml (53% of calculated average bladder size). After filling the bladder, the aim was to wait for 10 min after which the bladder was emptied through the catheter. In case VUR was detected, the bladder was immediately emptied. The scintigraphy imaging was started just after the radiopharmaceutical injection and continued long enough up to a maximum of one hour. If the child voided during the filling phase, the reinjection of 20 MBq of ^{99m}Tc -pertechnetate was given and the bladder filling was restarted. Two patients received a third bladder filling. DRC implementation followed the published guideline [11].

The effective doses for DRC were estimated by using the age- and activity-specific coefficients published by Stabin and Gelfand [13]. The effective doses were individually calculated based on the duration of exposure estimated from image data and administrated activity used in DRC examinations.

As of 2023, the costs for VCUG and DRC in our hospital were 296 euros and 679 euros, respectively.

Statistical analyses

Continuous variables were described with medians and IQR or range of values and in case of categorical variables percentages and frequencies were used. Difference between DCR and VCUG in radiation doses and bladder filling rates were compared using Wilcoxon signed rank test. Two-sided p -values less than 0.05 were considered statistically significant. Statistical analyses were carried out using the SAS® system for Windows, version 9.4. (SAS Institute Inc., Cary, NC, USA).

Ethics

The study received approval from the Turku University Hospital Clinical Research Center (Permission no: J13/20). It was conducted as a retrospective register study, and participants were not contacted, negating the need for informed consent or ethics committee approval. The processing of personal data was legally grounded in the public interest and scientific research, following the EU General Data Protection Regulation

2016/679 (Article 6(1)(e) and Article 9(2)(j)), and the Data Protection Act (Sections 4 and 6).

Results

Between 2011 and 2020, 204 patients underwent VCUG or DRC. 157 patients met the inclusion criteria for this study. One patient was excluded from the study as an outlier due to abnormally large radiation dose in the VCUG. Analyzes were performed on 156 patients. The radiation burden received by 24 patients could not be clarified retrospectively due to missing information on the device that had been used.

The cohort comprised 84 girls (53.8%) and 72 boys (46.2%), with a median age of 0.75 years (IQR 1 [0.38-1.33]). The primary indications for examination were urinary tract infection in 111 (71.2%) patients, antenatal hydronephrosis (AHN) in 42 (26.9%) patients and other causes (such as dysplastic kidney, urinary incontinence) in 3 (1.9%) patients. We excluded 23 patients suspected of having posterior urethral valves (PUV), 8 with trauma, fistula, or lower urinary tract anomalies, and 16 due to prior VUR examinations.

Among the study participants, 33 (21.2%) presented with urinary tract anomalies: duplex systems in 17 patients (10.9%); ureterocele in 2 (1.3%); and a combination of ureterocele and duplex system in 2 (1.3%) patients. Renal anomalies were identified in 5 patients (3.2%), including ARPKD, MCKD, renal dysplasia, atrophy, and agenesis on the contralateral side; vesico-ureteral junction stenosis was observed in 7 patients (4.5%).

Primary outcome: The effectiveness of using DRC for initial vesicoureteral reflux screening to minimize radiation exposure.

DRC was performed on 122 patients (78.2%), while VCUG was conducted on 96 patients (61.5%). Solitary DRC was carried out for 60 patients (38.5%) and solitary VCUG for 34 patients (21.8%). A combination of DRC and VCUG was applied in 62 cases (39.7%).

Direct radionuclide cystography identified VUR in 43 out of 122 patients (35%). Among these, VUR was right-sided in 15 patients (34.9%), left-sided in 17 patients (39.5%), and bilateral in 11 patients (25.6%). Despite negative results from DRC, 19 patients were further evaluated with VCUG due to factors like insufficient bladder filling, abnormal renal positioning, or unclear initial cystography results, revealing VUR in only one patient. DRC detected VUR in 6 patients (9.7%) with negative VCUG results.

VCUG findings showed VUR in 59 out of 96 patients (61.4%), with the condition being right-sided in 12 patients (20.0%), left-sided in 18 patients (30.0%), and bilateral in 29 patients (49.0%). The median VUR grade was 3.0 (range 1-5) on the left and 4.0 (range 1-5) on the right.

Regarding bladder filling rates in all patients, the median rate in DRC was 55 % (range 10-119%), while in VCUG it was 80% (range 15-233%). Patients who underwent both examinations filling rate was 37% in DRC and 67% in VCUG ($p < 0.0001$).

Secondary outcome: Radiation burden caused by VUR diagnostics

The median effective radiation dose observed in all patients in DRC was 0.073 mSv (range 0.014-0.363 mSv), while VCUG yielded a median effective dose of 0.023 mSv (range 0.007-0.168 mSv). For patients who underwent both examinations, the median effective radiation dose observed in DRC was 0.063 mSv (range 0.014-0.344 mSv), while VCUG yielded a median effective dose of 0.023 mSv (range 0.007-0.168 mSv) $p < 0.0001$ (Fig. 1). When both examinations were necessary, the median effective dose amounted to 0.098 mSv (range 0.014-0.419 mSv). The variation between the two median effective doses reflects differences in the subsets of patients who underwent only DRC versus those who required both examinations.

In the age group under one year, 69 patients were examined by VCUG. The median DAP in the group was $3.60 \mu\text{Gym}^2$ (range 0.84-29.4 μGym^2). The age group 1 to 2 years included 13 patients, and the median DAP was $2.76 \mu\text{Gym}^2$ (range 1.00-14.6 μGym^2), and in the group over 2 years old there were 11 patients, and the median DAP was $9.52 \mu\text{Gym}^2$ (range 1.86-50.4 μGym^2). The median effective doses were representatively 0.023 mSv (range 0.09-0.32 mSv), 0.021 mSv (range 0.007-0.090 mSv), and 0.032 mSv (range 0.014-0.168 mSv). The effective dose information was not calculated for 4 patients because of the examination dose report was missing from the patient database.

Discussion

Vesicoureteral reflux (VUR) is a complex condition with variable symptoms and potential long-term consequences, making early and accurate diagnosis crucial. It is primarily caused by a deficient closure mechanism at the ureterovesical junction and inefficient ureteral dynamics. Traditional diagnostic methods encompass radiation exposure, which has led to the development of alternative methods. We show here that DRC, introduced to limit radiation exposure, usually entails a higher burden to the patient. We observed a lower median radiation dose in VCUG than in DRC in all age groups. While DRC can confirm or exclude the presence of VUR, a positive result necessitates a complementary VCUG, resulting in a median radiation dose of 0.098 mSv (0.014-0.419 mSv).

Our study used DRC as an initial screening tool, identifying VUR in 35% of the patients. Conversely, VCUG, conducted following DRC or as an independent diagnostic measure, detected VUR in approximately 61% of cases. This might indicate a higher detection rate with VCUG. However, the selection for VCUG was likely influenced by preliminary DRC findings, potentially skewing this comparison. Notably, when combining DRC and VCUG, our approach aimed to balance the need for diagnostic accuracy with minimizing patient exposure to radiation. Our cohort's overall VUR detection rate was approximately 49%, underscoring the complementary roles of DRC and VCUG in our diagnostic arsenal. Primary indications for these examinations included urinary tract infections and antenatal hydronephrosis (AHN), highlighting the clinical scenarios where these diagnostic tools prove most valuable. Our study's approach reflects a stratified diagnostic pathway, where DRC served as an initial filter,

subsequently guiding the more targeted use of VCUG to confirm and classify VUR in selected cases. Our study, however, reveals that the effective radiation dose associated with DRC was, in fact, higher than that created by VCUG. This discrepancy was further magnified when both studies were combined for VUR grading. The median effective radiation dose observed for DRC across all patients was 0.073 mSv. However, for the subset of patients who underwent both DRC and VCUG, the median radiation dose for DRC was slightly lower, at 0.063 mSv. This difference reflects the variations in patient cohorts, with those undergoing both studies likely receiving lower overall doses during DRC due to different clinical circumstances or the need for early termination of the examination when VUR was identified. These results are consistent with those reported by Haid et al., who found a median effective radiation dose of 0.085 mSv for DRC, while VCUG ranged from 0.008 to 0.018 mSv [14]. Previous studies have also reported effective doses for VCUG ranging from 0.03 to 0.3 mSv [10]. Notably, advancements in modern image acquisition tools and protocol optimization have reduced the VCUG radiation dose.

Originally developed to reduce radiation exposure in screening for vesicoureteral reflux, DRC, as a primary assessment tool, must be viewed in light of its constraints, including a higher radiation dose than VCUG and an inherent inability to provide anatomical details. In contrast, VCUG has through optimized protocols a more favorable radiation profile and offers anatomical delineation, providing insights for comprehensive assessment and management of VUR. Consequently, the evidence from our study further underscores the diminished role of DRC in modern diagnostic regimens. It affirms VCUG as the preferred method due to its dual advantages of lower radiation exposure and superior diagnostic detail. This shift towards VCUG aligns with the

evolving standards of patient care, emphasizing the necessity of anatomical clarity and minimizing radiation risk. Additionally, cost analysis reinforces this choice, showing that VCUG is more cost-effective than DRC with DRC incurring an additional expense of approximately 345 euros per patient in our cohort. However, the cost estimate should be viewed as an indicative estimate rather than a universally applicable figure. Taken together, this underscores the need for a judicious approach to selecting diagnostic tools, integrating both clinical outcomes and financial considerations in pediatric urological evaluations. While contrast-enhanced ultrasound-based methods like CEVUS have shown efficacy in VUR diagnostics, their current capabilities may not extend to detailing specific measurements such as the ureteral diameter ratio [15]. Therefore, VCUG retains its role in VUR diagnostics, offering unparalleled anatomical clarity.

While our findings highlight the limitations and obsolescence of DRC in the face of VCUG capabilities, it is pertinent to acknowledge previous studies that have outlined the utility of DRC in specific contexts. Dalirani et al. [16] highlighted DRC's heightened sensitivity over VCUG in a cohort of 35 patients with UTIs and previously negative VCUG results. Similarly, Saraga et al. [17] reinforced the sensitivity of DRC in detecting VUR missed by VCUG, noting its ability to trace reflux up to the renal pelvis—a detail VCUG occasionally missed. Our observations of DRC identifying VUR in 6 (9.7%) cases where VCUG did not align with these reports suggest a nuanced role for DRC in VUR detection. However, the broader applicability and clinical implications of this sensitivity remain subjects for further exploration. Notably, low-grade VUR often requires no intervention without other risk factors [5]. Moreover, Sükan et al. found no significant difference in VUR detection between DRC and VCUG but posited DRC's potential advantages for younger children [18]. Unver et al. maintained that

despite the diagnostic equivalency of DRC and VCUG, the former might be preferable in scenarios where reducing gonadal radiation and facilitating continuous monitoring are priorities [19]. These perspectives underscore a complex landscape where DRC's specific benefits warrant consideration of its shortcomings, especially in tailored clinical scenarios.

Despite the obsolescence of DRC due to its higher radiation dose and lack of anatomical detail, it is noteworthy that DRC was associated with lower bladder filling (55%) volumes compared to VCUG (80%). This difference may have clinical relevance, as excessive bladder filling during VCUG could induce iatrogenic reflux, potentially leading to unnecessary interventions and increased risk of complications. However, conclusive evidence on this aspect is still pending. The potential for iatrogenic reflux underscores the need for careful consideration of bladder-filling practices to mitigate undue treatment and complication risks.

Ionizing radiation exposure is associated with an elevated risk of cancer with children exhibiting greater radiation sensitivity than adults [20, 21]. A 1-year-old infant is 10-15 times more likely to develop cancer following radiation exposure when compared to adults [21]. The radiation levels from DRC and VCUG examinations entail low radiation doses compared to the detriment-adjusted cancer risk proposed by International Commission on Radiological Protection (ICRP): $5.5 \cdot 10^{-2}$ per mSv [22]. Compared to the background radiation of approximately 1 mSv per year, these examinations represent exposing an excess dose from a week (VCUG) to 2.5 weeks (DRC). However, due to the long expectable lifetime of children and their elevated

sensitivity to radiation, one should restrict their exposure to as low as reasonably practicable (ALARP).

This study has limitations. First, the lack of a standardized protocol for VUR imaging across the study period led to significant variability, including bladder filling volumes and imaging techniques between DRC and VCUG. In effective dose estimations for DRC, bladder filling volumes and patient body sizes were not individually modelled. Instead, typical approximations were used. Furthermore, during the study years, VCUG was conducted using various types of equipment, potentially leading to variations in the radiation doses received by patients. Administrated activity used in DRC was also based on a more than 20-years old guideline, which creates a potential to optimize radiation exposures of DRC technique in the future [11]. These factors introduce challenges to the generalizability of our study results.

Despite these limitations, the study has notable strengths. We diligently collected patient profiles, including background information and follow-up data. VCUG radiation doses were accurately calculated by medical physicist considering the impacts of different devices and differences in the implementation of methods on radiation exposure. This careful approach to data collection and radiation assessment ensures the reliability and accuracy of our findings. Nevertheless, further research is required to clarify patient-specific radiation doses between the different imaging modalities.

Conclusion

Our study underscores that contrary to its designed purpose of minimizing radiation exposure, DRC may subject patients to a more significant radiation load compared to VCUG. Additionally, the enhanced ability of DRC to detect VUR requires subsequent VCUG confirmation for positive findings, thereby increasing the overall radiation exposure experienced by patients. These observations call into question DRC's viability as a preferable low-radiation option for screening pediatric VUR.

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Figure legends

Figure 1. Effective dose (ED) scatter plot. The ED is presented in y-axis (mSv), and the patient number in age order of age in x-axis. The blue dots represent the EDs from DCR and orange dots from VCUG.

To:

September 27th, 2024

Editor Christopher Marshall

Nuclear Medicine Communications

Dear Editor Christopher Marshall,

We thank you for giving us the possibility to clarify this inconsistency. We have revised the manuscript to clarify the median radiation doses. All changes are highlighted in green in the manuscript and listed in detail below. We hope this addresses the reviewer's concern and remain available for any further corrections if necessary.

Comment: Thank you for resubmitting NMC-11-5267R1. Having corresponded with the reviewer, we are still not sure you have fully resolved the issue raised with regards to. The median effective radiation dose in DRC is 0.063 mSv, while in the results section of this manuscript it has been stated as 0.073 mSv. Please verify this issue. The reviewer is still unclear as to whether the median effective Radiation dose in DRC 0.063 or 0.073 mSv. The median dose for all patients who underwent DRC was 0.073 mSv whilst the median DRC dose for all patients who underwent both DRC and VCUg was 0.063 mSv. Both the reviewer and myself feel that the 0.073 mSv is the correct median dose for DRC. Can you explain why there is a difference between the two doses to justify stating the median dose in DRC is 0.063 mSv if you still wish to use this value.

Reply: We have revised the manuscript to clarify the median radiation doses, specifying that the 0.063mSv applies to patients with VUR identified in DRC who subsequently underwent VCUg.

Abstract: "Median radiation doses were lower in VCUg (0.023 mSv) than in DRC (0.073 mSv). For patients requiring complementary VCUg after DRC, the median radiation dose for DRC was 0.063 mSv ($p < 0.0001$), resulting in a total median dose of 0.098 mSv. "

Results: "The variation between the two median effective doses reflects differences in the subsets of patients who underwent only DRC versus those who required both examinations"

We also write the introduction section of the abstract shorter so that the number of words remained below the required amount

Best regards,

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