BIOMEDICAL JOURNAL 44 (2021) S226–S234

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Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Original Article

# Bladder volume reproducibility after water consumption in patients with prostate cancer undergoing radiotherapy: A systematic review and meta-analysis

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ARTICLE INFO

*Article history:*
Received 9 January 2020
Accepted 2 November 2020
Available online 4 November 2020

*Keywords:*
Bladder volume
Reproducibility
Prostate cancer
Radiotherapy

ABSTRACT

*Background:* To minimize toxicity due to radiotherapy in patients with prostate cancer, high bladder volume reproducibility is essential. Water consumption is often used to increase bladder volume reproducibility, but the optimal amount of water required to be consumed remains unclear. We aimed to analyzed the relationship between water consumption and bladder volume reproducibility in patients undergoing radiotherapy for prostate cancer.
*Methods:* We conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies that assessed bladder volume change after water consumption in patients with prostate cancer undergoing radiotherapy. MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched for relevant studies published from database inception up until July 4, 2020. The Newcastle–Ottawa Scale was used to evaluate the risk of bias in the included studies. The outcome was the mean difference (MD) of bladder volume after water consumption, evaluated through meta-analysis using a random-effects model.
*Results:* Ten cohort studies and one randomized controlled trial with a total of 417 patients were included. For 300–400 ml water consumption, the bladder volume MD between during treatment and at computer tomography-simulation (95% confidence interval [CI]) was −11.97 (−51.68 to 27.74), was −45.99 (−82.85 to −9.13) for 500–540 ml water consumption and −45.92 (−78.86 to −12.98) for water consumption until full-bladder sensation was reached.

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Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2020.11.004

*Conclusion:* Consuming 300–400 ml of water potentially leads to the best bladder volume reproducibility; moreover, the higher the water consumption volume, the lower the bladder volume reproducibility.

## At a glance of commentary

*Scientific background on the subject*

Radiotherapy is a treatment option for prostate cancer. Patients with prostate cancer receiving radiotherapy are instructed to maintain a full bladder to reduce bladder toxicity and increase treatment reproducibility. However, older patients may have difficulty achieving full bladder and may not be able to maintain their bladder volume during radiotherapy.

*What this study adds to the field*

Water consumption is used to increase bladder volume reproducibility, but the optimal amount of water to be consumed remains unclear. We searched and analyzed the relation between water consumption and bladder volume in radiotherapy for prostate cancer. Consuming 300-400 ml of water was associated with the best bladder volume reproducibility.

Radiotherapy is one of the most effective treatments for cancer. The goal of radiotherapy is to achieve high local tumor control (tumor control probability) with a low risk of normal tissue complications (normal tissue complication probability) [1]. Prostate cancer had the third highest increase rate among all cancers in Taiwan in 2016. According to the Department of Health Promotion Administration, and Ministry of Health and Welfare in Taiwan, 5359 incident cases of prostate cancer were noted in 2016, with 944 patients requiring radiotherapy [2]. However, the incidence of prostate cancer in the United States was 160,000 patients [3]. Water consumption has been advocated before receiving radiotherapy for prostate cancer [4–6]. Patients with prostate cancer treated with radiotherapy are instructed to maintain a full bladder to reduce bladder toxicity [7–11] and to increase treatment reproducibility. However, older patients may have difficulty arriving with full bladder and may not be able to maintain their bladder volume during radiation treatment.

During radiotherapy for prostate cancer, three aspects of the bladder vary: volume, shape, and the distance between the bladder and the prostate. This study focused on bladder volume change. Bladder volume reproducibility refers to the maintenance of the same bladder volume in every radiation treatment. High bladder volume reproducibility minimizes the error of radiotherapy for prostate cancer.

Patients should ideally maintain a full bladder if possible, but the bladder volume in patients with prostate cancer was reported to be unknown [12,13]. However, an increased bladder volume in the high-dose region loops resulted from treatment plans which were conducted with an empty bladder [5,6]. Maintaining a full bladder can thus enable the clinical application of a “full bladder” protocol. Bladder volume reproducibility is typically enhanced through water consumption, but the optimal amount of water to be consumed remains unclear. Bladder volume consistency is beneficial for the execution of a radiotherapy course.

The current study analyzed the relation between water consumption and bladder volume in radiotherapy for prostate cancer by conducting a systematic review and meta-analysis of relevant studies.

## Methods and materials

Observational studies, including cohort studies and randomized controlled trials (RCTs), on the association of water consumption and bladder volume in patients with prostate cancer undergoing radiotherapy were included. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] and the Meta-analysis of Observational Studies in Epidemiology [15] guidelines. The International Prospective Register of Systematic Reviews (PROSPERO) registration number for this study is CRD42019130100. MEDLINE, Cochrane Central Register of Controlled Trials, and Embase were searched for relevant studies published from database inception up until July 4, 2020; the search did not include language or geographical restrictions. The search strategy is presented in [Table 1].

Only studies meeting the following criteria were included: (1) being an observational cohort study or RCT that examined the water consumption-bladder volume association in patients with prostate cancer undergoing radiotherapy; (2) including only human participants; (3) assigning only patients with prostate cancer to both the case and control groups; (4) ensuring that water consumed (ml) before radiotherapy varied; and (5) measuring bladder volume using a computer tomography (CT) simulator or an ultrasonic (US) device. Two authors (H.C. and K.L.) independently screened and assessed the eligibility of the studies by reviewing their titles and abstracts. They then reviewed the full text of the potentially eligible studies and selected studies meeting the inclusion criteria. Any disagreement was resolved by consulting the third author (C.C.) [16].

The following data were extracted from the included studies: first author, year of publication, country, study design, and quantitative estimates, including mean difference (MD) for the association of water consumption with prostate cancer. We used the Newcastle–Ottawa Scale to assess the risk of bias of included studies [17]. The following eight domains were evaluated for the included cohort studies: representativeness of exposed cohort, selection of a non-exposed cohort, ascertainment of exposure, outcome of the interest

**Table 1 Search strategy.**

| | |
|---|---|
| **Cochrane Central Register of Controlled Trials (CENTRAL) search strategy** | |
| #1 | prostate cancer:ti,ab,kw (Word variations have been searched) |
| #2 | MeSH descriptor: [Prostatic Neoplasms] explode all trees |
| #3 | #1 or #2 |
| #4 | Radiotherapy:ti,ab,kw (Word variations have been searched) |
| #5 | MeSH descriptor: [Radiotherapy, Image-Guided] explode all trees |
| #6 | #4 or #5 |
| #7 | Full bladder:ti,ab,kw (Word variations have been searched) |
| #8 | Bladder filling:ti,ab,kw (Word variations have been searched) |
| #9 | #7 or #8 |
| #10 | Empty rectum:ti,ab,kw (Word variations have been searched) |
| #11 | #9 or #10 |
| #12 | #3 and #6 and #11 |
| **MEDLINE search strategy** | |
| 1. | prostate cancer.mp |
| 2. | exp prostate neoplasms/ |
| 3. | 1 or 2 |
| 4. | Radiotherapy.mp |
| 5. | Exp radiotherapy, Image-guide/ |
| 6. | 4 or 5 |
| 7. | Full bladder.mp |
| 8. | Bladder filling.mp |
| 9. | 7 or 8 |
| 10. | Empty rectum.mp |
| 11. | 9 or 10 |
| 12. | 3 and 6 and 11 |
| **Embase search strategy** | |
| #1 | ‘prostate cancer’ |
| #2 | ‘prostate neoplasms’/exp |
| #3 | #1 or #2 |
| #4 | ‘radiotherapy’ |
| #5 | ‘image guided radiotherapy’/exp |
| #6 | #4 OR #5 |
| #7 | ‘full bladder’ |
| #8 | ‘bladder filling’ |
| #9 | #7 OR #8 |
| #10 | ‘empty rectum’ |
| #11 | #9 OR #10 |
| #12 | #3 AND #6 AND #11 |

not present at the start of study, comparability of cohorts, and assessment of outcome, follow-up duration, and adequacy of the follow-up of cohorts. We used the Cochrane Collaboration's tool to assess the risk of bias of the RCT [16]. For this assessment, the following seven domains were evaluated for the included RCT: random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias sources.

The included studies tested the following volume of water consumption: 300 ml, 350 ml, 400 ml, 500 ml, 540 ml, 1080 ml and comfortable full bladder. As there are no specific consensus cut-off criteria for water consumption, we decided to divide into the following four groups to investigate their effects on bladder volume reproducibility: 300–400 ml, 500–540 ml, 1080 ml, and full bladder.

All analyses were conducted using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We calculated the pooled MD in bladder volume along with the corresponding 95% confidence interval (CI) for the included RCT and cohort studies. If multiple risk estimates were provided in the study report, we adopted the risk estimates with the most adjusted confounders. The statistical heterogeneity across the included studies was assessed using the $I^2$ statistic, with $I^2 > 50\%$ being considered to represent moderate heterogeneity. The DerSimonian and Laird random-effects model was adopted for conducting the meta-analysis because clinical heterogeneity was anticipated [16].

## Results

The PRISMA study flowchart is presented in [Fig. 1]. Our search identified 345 articles after the removal of duplicates. After the titles and abstracts were scanned, 328 citations were excluded. Additionally, after examining the articles by their titles, we included 11 studies in our qualitative synthesis and meta-analysis. One study did not have data on standard deviation. Finally, 1 RCT and 10 cohort studies, with a total of 417 participants, were included [18–28]. The characteristics of the included cohort studies [18–27] and the RCT [28] are listed in [Tables 2 and 3], respectively.

The risk of bias of included cohort and RCT studies is summarized in [Fig. 2]. All included cohort studies [18–27] were rated as having a low risk of bias in selection categories because the study groups included patients with prostate cancer. Four studies [18,19,22,24] were rated as having an unclear risk in the domain of the outcome of interest not present at the start of the study. The reason was that the bladder was not emptied before drinking and the bladder condition was unknown. Three studies [18,19,24] were rated as high risk in the domains of comparability of cohorts and adequacy of the follow-up of cohorts. The main reason for the high risk in the comparability of cohorts was that study controls were not designed to control hydration and waiting time. Moreover, the high risk of bias in the adequacy of the follow-up of cohort domain [21] was because the follow-up rate was <80% and because patients lost in the process of follow-up were not specified. Regrading critical appraisal, all studies included in the meta-analysis scored well on the Newcastle–Ottawa Scale and the Cochrane Collaboration's tool. All included patients with prostate cancer undergoing a radiation treatment loop. Because the compliance of the treated patients was high, extensive research data could be collected. All measurements were performed using a CT simulator or US device, which considerably reduced human interference.

[Fig. 3] illustrates the forest plots of the MD in the consumption of different volumes of water. We divided patients in all studies into four groups according to generalized water consumption criteria and then examined the groups. Groups 1, 2, and 3 were comprised of patients who consumed 300–400 ml [22,25,27], 500–540 ml [20,21,23,26,28], 1080 ml [28] of water ($I^2 = 0\%$, 39%, and 0%), respectively, and Group 4 was comprised of those with full bladders [18,19,24,25] ($I^2 = 33\%$). Stratification of studies based on different volumes of water consumption resulted in similarly low heterogeneity levels ($I^2 < 50\%$).

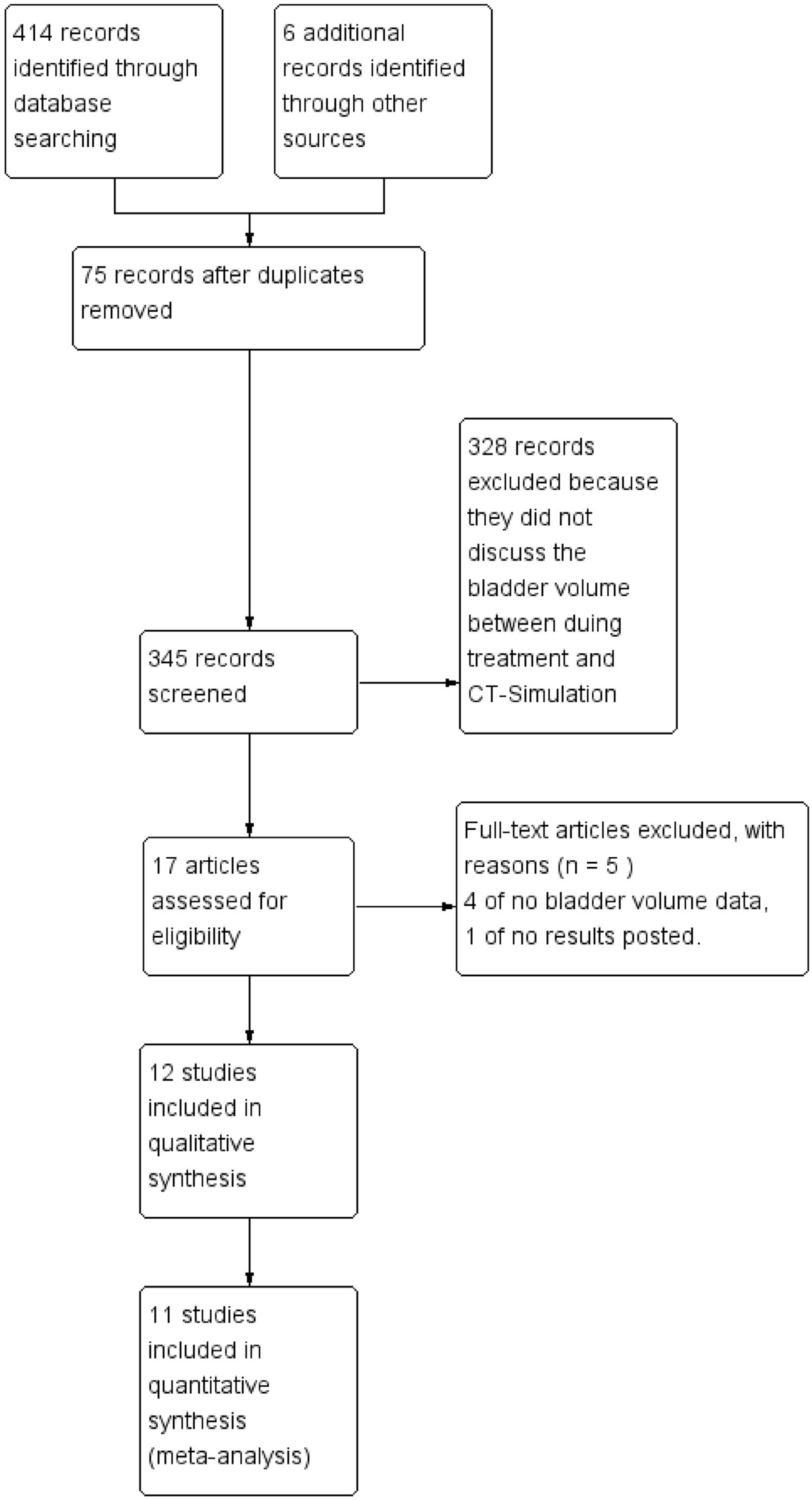


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flowchart.

**Table 2 Characteristics of included cohort studies.**

| Source | Study Design | No. of patients | No. of bladder volume measurements taken | Bladder filling instructions | Mean difference ± SD | | Types of radiotherapy |
|---|---|---|---|---|---|---|---|
| | | | | | Treatment planning computed tomography | During treatment | |
| Braide et al. [27],2019 | Cohort | 13 | 6–8 | Void, 300 ml, wait 60 min | 159.27 ± 100.34 ml | 147.93 ± 62.28 ml | – |
| O'Doherty et al. [25], 2006 | Cohort | 41 | 8 | Void, 350 ml, wait 60 min | 362 ± 229 ml | 240 ± 166 ml | – |
| Casares-Magaz et al. [22], 2017 | Cohort | 27 | 9–10 | 400 ml | 217 ± 134 ml | 193 ± 78 ml | IMRT and VMAT |
| Li et al. [20], 2015 | Cohort | 16 | 13–14 | Void, 500 ml, wait 30 min | 161.25 ± 116.87 ml | 160.74 ± 82.47 ml | IMRT |
| Ho et al. [21], 2016 | Cohort (Retrospective) | 28 | 4 | Void, 500 ml, wait 45 min | 318.88 ± 138.08 ml | 223.62 ± 138.08 ml | IMRT |
| Nathoo et al. [23], 2018 | Cohort (Prospective) | 26 | 5 | Void, 500 ml, wait 30 min | 335.3 ± 158.4 ml | 292.8 ± 117.64 ml | SABR |
| Hynds et al. [26], 2011 | Cohort | 30 | 37 | Void, 500 ml in 15 min, wait 30 | 282 ± 144 ml | 189 ± 134 ml | 3DCRT |
| O'Doherty et al. [25], 2006 | Cohort | 25 | 8 | Comfortable full bladder | 286 ± 164 ml | 308 ± 197 ml | – |
| Stam et al. [24], 2006 | Cohort | 18 | 30 | Full bladder | 348 ± 237 ml | 250 ± 149 ml | 3DCRT |
| Stam et al. [24], 2006 | Cohort | 16 | 30 | Full bladder | 367 ± 202 ml | 313 ± 156 ml | 3DCRT |
| Pinkawa et al. [19], 2007 | Cohort | 50 | 2–3 | Feeling full | 225 ± 131 ml | 217 ± 112 ml | – |
| Antolak et al. [18], 1998 | Cohort | 17 | 3 | Full bladder (no details) | 291.73 ± 42.66 ml | 250 ± 48.5 ml | – |

Abbreviations: 3DCRT: Three dimensional conformal radiation therapy; IMRT: intensity modulated radiation therapy; SABR: stereotactic ablative radiotherapy; VMAT: volumetric modulated arc therapy.

**Table 3 Characteristics of included randomized controlled trial.**

| Source | Study Design | No. of patients | No. of bladder volume measurements taken | Bladder filling instructions | Mean difference ± SD | | Types of radiotherapy |
|---|---|---|---|---|---|---|---|
| | | | | | Treatment planning computed tomography | During treatment | |
| Mullaney et al. [28], 2014 | RCT | 50 | 23 | Void, 540 ml in 10 min, wait 30–40 min | 181 ± 121 ml | 162 ± 98 ml | 3DCRT |
| Mullaney et al. [28], 2014 | RCT | 60 | 23 | Void,1080 ml in 10 min, wait 30–40 min | 262 ± 171 ml | 227 ± 126 ml | 3DCRT |

Abbreviations: 3DCRT: Three dimensional conformal radiation therapy; RCT: randomized controlled trial.

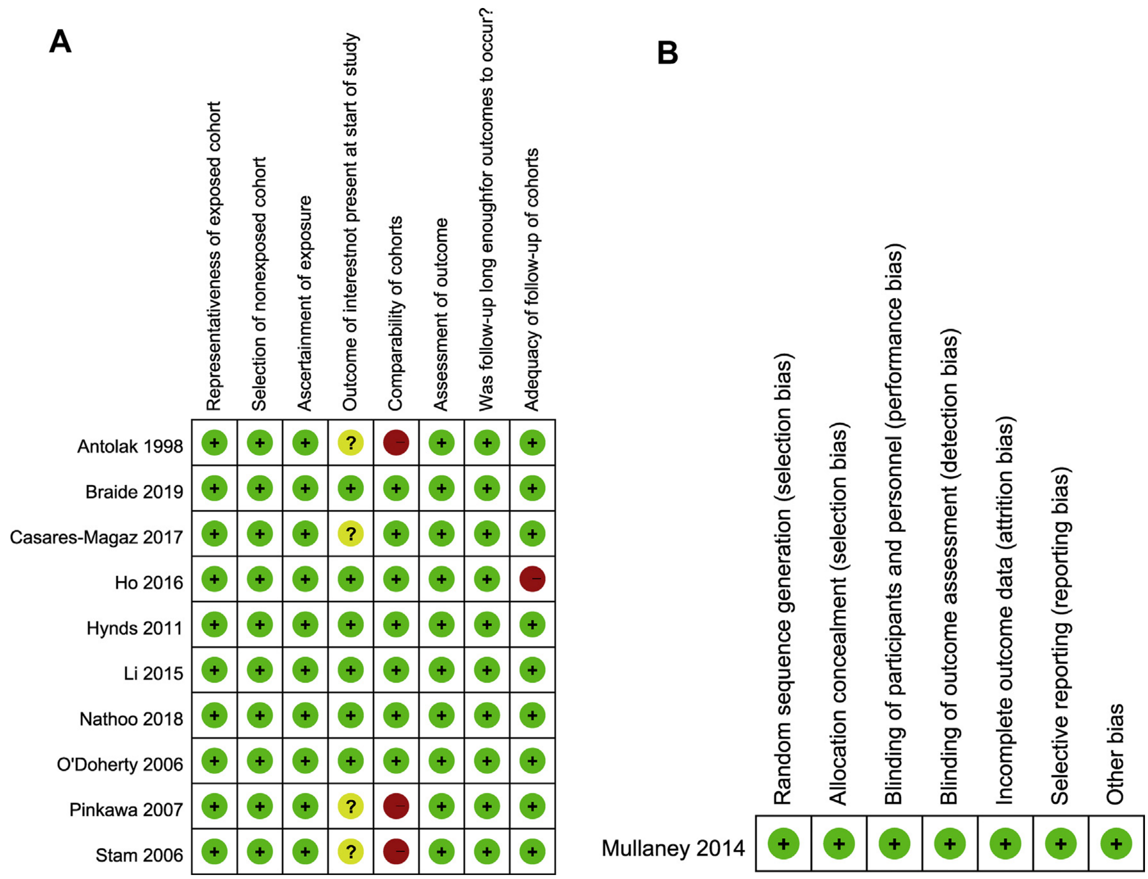


Fig. 2 (A) Risk of bias of included cohort studies. (B) Risk of bias of included randomized controlled trial. The green, yellow, and red dots denote low, unclear, and high risks of bias, respectively.

To compare the groups' bladder volumes, we computed the pooled MD in bladder volume measured during CT simulation and observed no significant difference [22,25,27] between Group 1 (pooled MD -11.97; 95% CI -51.68 to 27.74) and Group 3 (MD -35.00; 95% CI -88.75 to 18.75). Significant changes in bladder volume were noted in Group 2 (MD -45.99; 95% CI -82.85 to −9.13) and Group 4 (MD -45.92; 95% CI -78.86 to −12.98). The results did not substantially change when we excluded four studies rated with high risk of bias (data not shown) [18,19,21,24]. No publication bias was detected in the funnel plot [Fig. 4] [16].

## Discussion

According to our review of the literature, this study is the first meta-analysis to examine the association of water consumption with bladder volume in patients with prostate cancer undergoing radiotherapy. The bladder volume of patients consuming 300–400 ml of water exhibited minimal difference between treatment and CT simulation statuses. Consuming 300–400 ml of water was associated with the best bladder volume reproducibility. Drinking 300–400 ml is considerably easier and more practical than drinking 500 ml, especially for Asians [29].

Only one cohort study reported the evaluation of bladder volume in Asian patients and demonstrated no significant difference (MD -0.51; 95% CI -70.6 to 69.58) [20]. In this study, more than 100 people were treated, and 16 patients were selected after meeting the selection criteria, which did not represent the majority. Other studies conducted in Western countries reported that consuming 300–400 ml of water was associated with the best bladder volume reproducibility (pooled MD -11.97; 95% CI -51.68 to 27.74) [22,25,27]. Although there was no statistically significant change in bladder volume in those consuming 1080 ml (Group 3), only one trial contributed data to this group [28] and more studies are needed to replicate the findings.

Thus, a detailed explanation of hydration objects can improve bladder reproducibility [26,28,30–32]. Regardless of the amount of water consumed, a consistent bladder volume is ideal. However, many studies have found that bladder volume during treatment was less than that during CT simulation [18–27]. The possible reason is that some people are worried about having a full bladder. Other studies have indicated that this was often the case during prostate treatment. The smallest possible bladder volume is recommended to increase comfort and efficiency [33,34]. To improve patient comfort and reproducibility, a method that would require a bladder volume of approximately 150 ml should be established.

Ultrasonic machines are efficient at assessing repeatability [23–25], but they require a range of conditions. If an ultrasonic machine is unavailable, the reproducibility of water consumption is required.

| Study or Subgroup | During tx Mean | During tx SD | During tx Total | At CT Mean | At CT SD | At CT Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.1.1 300-400 ml** | | | | | | | | |
| Braide 2019 | 147.93 | 62.28 | 13 | 159.27 | 100.34 | 13 | 38.3% | -11.34 [-75.54, 52.86] |
| Casares-Magaz 2017 | 193 | 78 | 27 | 217 | 134 | 27 | 46.1% | -24.00 [-82.48, 34.48] |
| O'Doherty 2006a | 308 | 197 | 25 | 286 | 164 | 25 | 15.6% | 22.00 [-78.48, 122.48] |
| **Subtotal (95% CI)** | | | **65** | | | **65** | **100.0%** | **-11.97 [-51.68, 27.74]** |
| Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (*p* = 0.74); I² = 0% | | | | | | | | |
| Test for overall effect: Z = 0.59 (*p* = 0.55) | | | | | | | | |
| **1.1.2 500-540 ml** | | | | | | | | |
| Ho 2016 | 223.62 | 138.08 | 28 | 318.88 | 138.08 | 28 | 17.3% | -95.26 [-167.59, -22.93] |
| Hynds 2011 | 189 | 134 | 30 | 282 | 144 | 30 | 18.0% | -93.00 [-163.39, -22.61] |
| Li 2015 | 160.74 | 82.47 | 16 | 161.25 | 116.87 | 16 | 18.1% | -0.51 [-70.60, 69.58] |
| Mullaney 2014b | 162 | 98 | 50 | 181 | 121 | 50 | 30.4% | -19.00 [-62.16, 24.16] |
| Nathoo 2018 | 292.8 | 117.64 | 26 | 335.3 | 158.4 | 26 | 16.3% | -42.50 [-118.34, 33.34] |
| **Subtotal (95% CI)** | | | **150** | | | **150** | **100.0%** | **-45.99 [-82.85, -9.13]** |
| Heterogeneity: Tau² = 678.77; Chi² = 6.54, df = 4 (*p* = 0.16); I² = 39% | | | | | | | | |
| Test for overall effect: Z = 2.45 (*p* = 0.01) | | | | | | | | |
| **1.1.3 1080 ml** | | | | | | | | |
| Mullaney 2014a | 227 | 126 | 60 | 262 | 171 | 60 | 100.0% | -35.00 [-88.75, 18.75] |
| **Subtotal (95% CI)** | | | **60** | | | **60** | **100.0%** | **-35.00 [-88.75, 18.75]** |
| Heterogeneity: Not applicable | | | | | | | | |
| Test for overall effect: Z = 1.28 (*p* = 0.20) | | | | | | | | |
| **1.1.4 Full bladder** | | | | | | | | |
| Antolak 1998 | 250.4 | 34.3 | 17 | 291.7 | 30.2 | 17 | 49.1% | -41.30 [-63.02, -19.58] |
| O'Doherty 2006b | 240 | 166 | 41 | 362 | 229 | 41 | 11.8% | -122.00 [-208.58, -35.42] |
| Pinkawa 2007 | 217 | 112 | 50 | 225 | 131 | 50 | 27.0% | -8.00 [-55.77, 39.77] |
| Stam 2006a | 313 | 156 | 16 | 367 | 202 | 16 | 6.2% | -54.00 [-179.06, 71.06] |
| Stam 2006b | 250 | 149 | 18 | 348 | 237 | 18 | 5.9% | -98.00 [-227.33, 31.33] |
| **Subtotal (95% CI)** | | | **142** | | | **142** | **100.0%** | **-45.92 [-78.86, -12.98]** |
| Heterogeneity: Tau² = 451.99; Chi² = 5.98, df = 4 (*p* = 0.20); I² = 33% | | | | | | | | |
| Test for overall effect: Z = 2.73 (*p* = 0.006) | | | | | | | | |

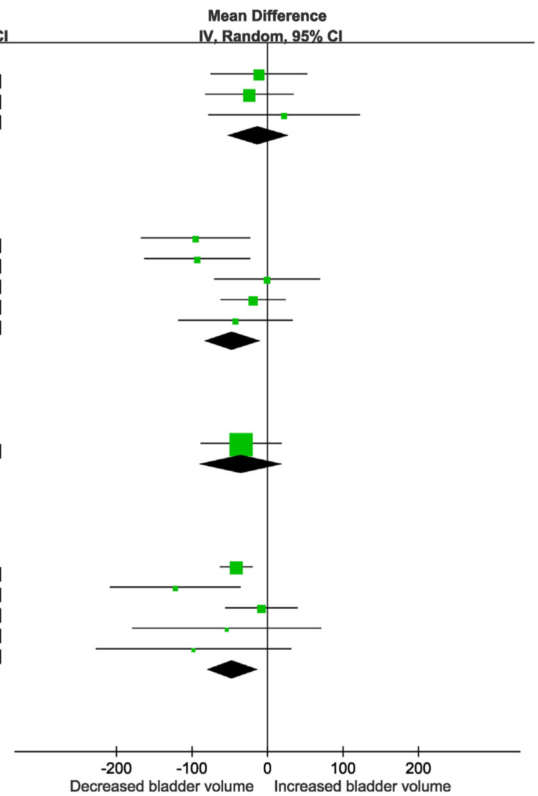


Fig. 3 Change in bladder volume after different volumes of water consumption. Abbreviations used: IV: inverse variance; MD: mean difference; SD: standard deviation.

This systematic review and meta-analysis has several limitations. First, the included studies did not provide a detailed explanation of their steps, except for the study by Mullaney et al. [28], showing that such steps may be a factor affecting bladder capacity determination. Second, the waiting time was not discussed in the current study. However, if a stable waiting time between CT simulation and treatment exists, this factor can be ignored. Third, studies considering water consumption of <300 ml were not included. Although this amount is more practical for Asians, many older people

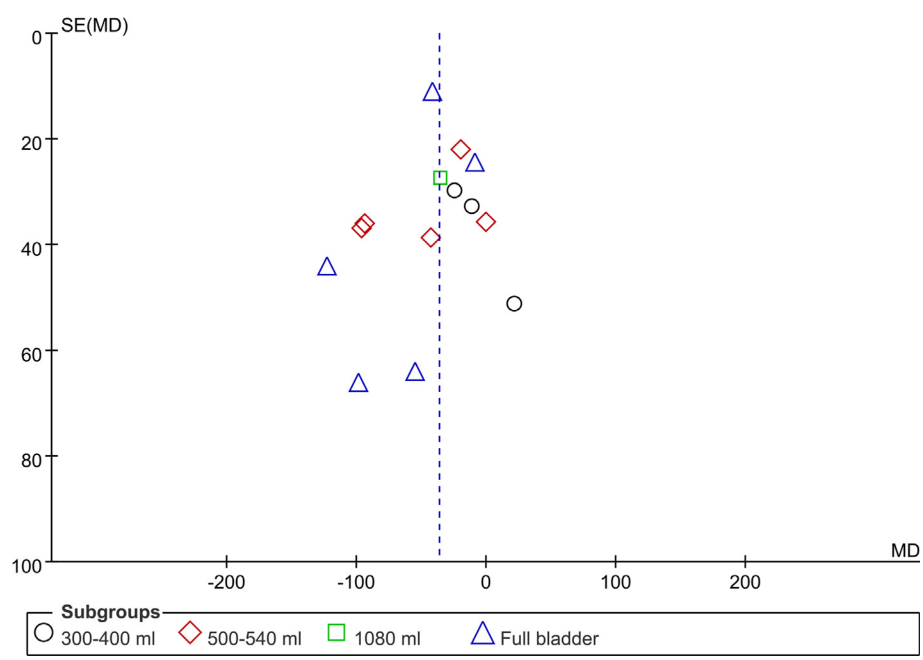


Fig. 4 Funnel plot. Abbreviations used: MD: mean difference; SE: standard error.

prefer not to drink too much water at once, and more evidence is required to discuss its advantages and disadvantages. Fourth, we failed to conduct subgroup analysis to address different types of radiotherapy and different prostate sizes due to lack of data.

## Conclusions

This study revealed that consuming 300–400 ml of water was associated with the best bladder volume reproducibility. In the future, we intend to determine the bladder volume reproducibility associated with drinking less than 300 ml of water.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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