Safely reduce cystoscopic evaluations for microscopic Hematuria patients (SeARCH Trial).

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To assess the clinical impact of implementing a molecular urine test in the diagnostic workup of patients presenting with microscopic hematuria.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON56042

Source
ToetsingOnline

Brief title
SeARCH Trial

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Bladder and bladder neck disorders (excl calculi)

Synonym
Microscopic hematuria, red blood cells in urine

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cost-effectiveness, microscopic hematuria, molecular urine test, patient-centered / value based

Outcome measures

Primary outcome

The primary endpoint is the net benefit of the *urine-first* strategy versus the *care-as-usual*, which is a cystoscopy in all patients presenting with microscopic hematuria. The net benefit is a decision analytic measure to evaluate the clinical implementation of an intervention commonly used in health.(17) In clinical decision models, the net benefit calculation determines whether implementing an intervention would do more good or harm (a positive value indicates a positive effect). This is achieved by putting the benefits (detection of a bladder tumor) and harms (performing diagnostic evaluation without any abnormal finding) on the same scale and multiplying the harms with a decision threshold. The decision threshold represents the estimated harms of the diagnostic intervention, such as the risk for a urinary tract infection, patients* burden, and use of available resources, against the harms of an outcome event, i.e. missing a bladder tumor. As previously reported, the decision threshold for evaluation of microscopic hematuria patients is determined at 3% (1 divided by 30). Meaning that a urologist is willing to conduct 30 cystoscopies to detect 1 bladder tumor.

Secondary outcome

The secondary outcomes are I) the number of cystoscopies and upper tract imaging modalities (CT or ultrasound) II) cost-effectiveness and III) patient

burden. These outcomes will be directly compared between the *care-as-usual* arm, a cystoscopy and upper tract imaging for all patients presenting with microscopic hematuria versus the *urine-first* strategy, in which only patients with an abnormal test result undergo diagnostic evaluation.

Study description

Background summary

Visual inspection of the bladder (cystoscopy) is commonly performed to rule out the presence of bladder cancer (BC) in patients presenting with microscopic hematuria.(2) However, only 2-3% of patients presenting with microscopic hematuria are diagnosed with bladder cancer, meaning that the majority of cystoscopies are redundant.(1, 5) The estimated direct medical costs of a cystoscopy is estimated to be $161-$222, which poses high burden on urological healthcare costs in addition to patient burden/discomfort.(4, 15) Moreover, the sensitivity of cystoscopy for the detection of bladder tumors is not 100%.(16) We propose to tackle these problems by performing a molecular urine test to triage microscopic hematuria patients for cystoscopy, a *urine-first* strategy. Due to the low incidence of bladder cancer in the microscopic hematuria population, three conditions have to be met for a urine test in this setting: i) the test must have a high negative predictive value (NPV) in order to prevent unnecessary invasive cystoscopies (urine test negative, absence of bladder tumor) ii) the test must have a high sensitivity for the detection of bladder cancer to minimize the number of false negative outcomes: i.e. urine test negative, presence of bladder tumor, and iii) the test must have a high specificity as this indicates the proportion of patients who unnecessarily undergo cystoscopy because of false-positive results.(19, 20) Given the robust test performance of the diagnostic urine assay in previous studies, the test seems to be an accurate diagnostic tool for the detection of bladder cancer in patients presenting with microscopic hematuria.(8) To justify clinical implementation of the novel urine test in daily practice, we argue that a direct comparison between the novel diagnostic strategy and care-as-usual is required.(14) Therefore, we propose to conduct a randomized controlled trial (RCT) to compare the clinical outcomes by implementing a *urine-first* strategy, in which only patients with an abnormal test result undergo a cystoscopic evaluation versus care-as-usual, which is a cystoscopy in all patients presenting with microscopic hematuria.

Study objective

To assess the clinical impact of implementing a molecular urine test in the diagnostic workup of patients presenting with microscopic hematuria.

Study design

A multicenter, prospective randomized controlled clinical trial in seven hospitals: Amphia ziekenhuis, Elisabeth-TweeSteden Hospital, Erasmus MC, Franciscus Gasthuis & Vlietland, Haga hospital, IJsselland hospital, Isala hospital, Rijnstate hospital, Treant zorggroep, and Onze Lieve Vrouwe Gasthuis.

Study burden and risks

The potential risk for patients in this study is a false negative exit test, i.e. two consecutive negative test results. In the three previous studies, the urine test had a robust performance for the detection of bladder cancer in microscopic hematuria with a consistent sensitivity >90% corresponding with negative predictive value (NPV) of >=99%. In a prior prospective study we conducted (N=838 patients), in which only a single urine assay was performed, the test result of the assay was false negative in only one out of 14 patients with microscopic hematuria. The tumor missed was a low risk bladder cancer (stage Ta Grade 1) with a very low risk for progression of disease.(8, 18) In the proposed study, the patient is asked to send in a second urine test which lower the possibility of a false negative test result. Although the chance of having a bladder tumor is extremely low (0.13%) after two consecutive negative urine tests, patients still have the possibility to undergo a diagnostic cystoscopy afterwards, if requested.
Implementation of a urine test as a triage tool for patients with microscopic hematuria has several beneficial effects;
I) The patient does not need to undergo a cystoscopy, which is an invasive procedure causing discomfort to the patient.(4, 9)
II) the assay might pick up upper urinary tract tumors, as the previous prospective study showed that the urine test detected all six upper urinary tract tumors.(8)
III) Only patients who are at high risk to have upper urinary tract cancer, i.e. positive test result but no abnormalities at cystoscopy are triaged to undergo imaging with CT, reducing the exposure to radiation in low risk patients.(11)
IV) Awareness of a positive urine test result significantly improves the bladder cancer detection rate at cystoscopy, i.e. diagnostic review bias.(12)
V) A *urine-first* strategy might be a more cost-effective approach.(13)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study a written informed consent is required. Thereby, a subject must meet the following criteria based on the most recent American Urological Association guideline on microscopic hematuria 2020.
- Microscopically confirmed microscopic hematuria of voided urine defined as >=3 erythrocytes per high power field
- Male patients >=40 years
- Female patients >=50 years

Exclusion criteria

- History of urothelial bladder- or urinary tract cancer
- Presence of macroscopic (visible) hematuria
- Woman who is or may be pregnant

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-05-2023
Enrollment:	1100
Type:	Actual

Medical products/devices used

Generic name:	Urine test
Registration:	No

Ethics review

Approved WMO Date:	12-12-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2023

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL77949.078.22