# Response evaluation after neoadjuvant chemotherapy for muscle invasive bladder cancer

No registrations found.

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|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Recruiting |
| **Health condition type** | - |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON25664

**Source**
Nationaal Trial Register

**Brief title**
PRE-PREVENCYS-trial

**Health condition**

Muscle-invasive bladder carcinoma

### Sponsors and support

**Primary sponsor:** Not applicable
**Source(s) of monetary or material Support:** Dutch Cancer Society

### Intervention

### Outcome measures

**Primary outcome**

The correlation between the clinical response (as assessed by clinical variables, radiological imaging, urine cytology and histological examination on per-operative TUR) and the final pathological response in the radical cystectomy (and lymph-node) resection specimen.

### Secondary outcome

1. The number of pathological complete responses (defined as ypT0N0 or ypTaN0 disease) after neo-adjuvant chemotherapy, 2. The number of participants in whom radical cystectomy could have been withheld if imaging, urine cytology and histological examination on transurethral resection was not followed by radical cystectomy, 3. Predictors of pathological complete response such as age, gender, clinical tumor stage, histological subtype, tumor size, radiological imaging, and a wideset of tissue and liquid biopsy genetic biomarkers.

## Study description

### Background summary

Rationale: Muscle-invasive bladder cancer (MIBC) is a highly aggressive disease with a 5year mortality rate of 40-50%. The gold standard of treatment of MIBC is neo-adjuvant chemotherapy plus radical cystectomy (RC), especially in patients with advanced stage disease. Interestingly, following neo-adjuvant chemotherapy at RC, a subset of patients (approximately 20-40%) has no evidence of disease. Patients who experience such a pathological complete response (pCR) have excellent survival. It might be that a subset of these patients do not benefit from radical surgery, which is a major surgical procedure. These patients might be candidates for active, close surveillance instead of having their bladder removed. At present, it is not yet possible to properly identify patients who have a pCR following neo-adjuvant chemotherapy and in whom radical surgery could be withheld.

Objective: To assess whether a pCR after neo-adjuvant chemotherapy can be predicted based on clinical, radiological, and histological variables and on a wide set of tissue and blood/urine (liquid biopsy) biomarkers (DNA/RNA). The results of this study will estimate the number of patients needed for a subsequent randomized controlled trial. The future so-called PREVENCYS trial will randomize patients into 2 strategy groups: (1) neo-adjuvant chemotherapy plus surgery, and (2) neo-adjuvant chemotherapy followed by an active surveillance.

Study design: Prospective cohort study, 36 months of inclusion.
Study population: Patients with stage cT2a-T4a N1 MIBC (urothelial cell carcinoma) who are planned to undergo neo-adjuvant cisplatin-based chemotherapy followed by RC are eligible. With an inclusion of 180 patients at baseline, approximately 60 patients will have a (complete) radiological response after neo-adjuvant chemotherapy and will undergo all procedures of the PRE-PREVENCYS trial including blood, urine and tissue collection, as well as a transurethral resection of suspicious lesions or scar tissue in the bladder at the time of RC.

Intervention: From all patients, blood and urine is prospectively collected for biomarker analyses on regular time intervals coinciding with clinical or outpatient visits. Just prior to RC on the day of surgery with the patient under general anesthesia, participants with a (complete) radiological response after neo-adjuvant chemotherapy will undergo cystoscopy

with bimanual examination, collection of urine cytology, and transurethral resection (TUR) of all visible lesions and/or scar tissue. Subsequently, RC with extended pelvic lymph node dissection is performed in all patients per local regular protocols, i.e. conventional open or robot-assisted laparoscopic RC. Tissue from the original diagnostic TUR, the TUR at RC, and the radical cystectomy specimen is examined for the expression of different biomarkers (DNA/RNA).

Main study parameters/endpoints: Using the outcome of the radiological and histological examination of both TUR's and the RC specimen, it is assessed: 1) To what extent the absence of residual disease by clinical (radiological imaging, urine cytology and cystoscopy + TUR) corresponds with a pCR in the RC specimen (to evaluate reliability of response evaluation), 2) What the number of pCR after neo-adjuvant chemotherapy is, 3) What the number of participants is in whom RC could have been withheld if imaging, urine cytology and cystoscopy + TUR showed absence of residual disease, 4) What predictors of pCR are, such as age, gender, clinical tumor stage, histological subtype, tumor size, radiological imaging. A special attention will be given to the assessment of tissue and liquid biopsy biomarkers.

**Study objective**

It is hypothesized that patients who have no radiological evidence of disease after neo-adjuvant chemotherapy, have absence of malignancy on transurethral resection of visible lesions and scar tissue in the bladder just before radical cystectomy. In addition, they have a biomarker profile that corresponds with urothelial cell carcinoma of low malignant potential and chemosensitivity and radical cystectomy could be withheld in these patients (bladder sparing approach).

**Study design**

Blood (and urine) collection will coincide with blood collections scheduled for routine care. Time points for blood and urine collection are: 1. At baseline, before start of neo-adjuvant chemotherapy 2. upon completion of neo-adjuvant chemotherapy, e.g. pre-surgery, 3. at first evaluation post-surgery at three months.

Tissue is examined for biomarker studies. Time points for tissue examination are 1. At diagnostic transurethral resection. Paraffin-embedded tissue is stored and collected retrospectively, 2. At the time of radical surgery, obtained by transurethral resection/biopsy during surgery, 3. Within the radical cystectomy specimen, if applicable.

**Intervention**

From all patients, blood and urine is prospectively collected for biomarker analyses on regular time intervals coinciding with clinical or outpatient visits. Just prior to radical cystectomy on the day of surgery with the patient under general anesthesia, participants with a (complete) radiological response after neo-adjuvant chemotherapy will undergo cystoscopy with bimanual examination, collection of urine cytology, and transurethral resection of all visible lesions and/or scar tissue. Subsequently, radical cystectomy with

extended pelvic lymph node dissection is performed in all patients per local regular protocols, i.e. conventional open or robot-assisted laparoscopic radical cystectomy. Tissue from the original diagnostic transurethral resection, the transurethral resection at radical cystectomy, and the radical cystectomy specimen is examined for the expression of different biomarkers (DNA/RNA).

# Contacts

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# Eligibility criteria

## Inclusion criteria

- 18 year and older
- Able to understand patient information form (PIF)
- Written informed consent, on study participation and for genomic testing
- Histological diagnosis of muscle-invasive bladder carcinoma i.e. cT2-T4a, WHO G1-G3 grade urothelial cell carcinoma of the bladder, locally confined or locally advanced
- Predominant histology is urothelial cell carcinoma (>50%)
- No evidence of regional or distant metastases, except for a single node in the surgical template of extended pelvic lymph-node dissection (cN1), on staging FDG-PET/CT before initiation of neo-adjuvant chemotherapy
- Indication for neo-adjuvant chemotherapy and radical cystectomy, as determined by local multidisciplinary tumor board,
- Cisplatin-based combination chemotherapy, i.e. ddMVAC or Gem-Cis per local hospital protocol
- Clinical response evaluation (CRE) by CT abdomen/thorax with contrast after the second cycle of neo-adjuvant chemotherapy (CRE1), and after completion of neo-adjuvant chemotherapy (CRE2) should show stable disease or a partial local radiological response (subgroup 1)
- CRE1 or CRE2 by CT scanning should show no evidence of residual tumor disease 9a

complete radiological response), which is defined as pelvic lymph nodes <10 mm in diameter showing no contrast enhancement and a bladder wall of <10 mm showing no contrast enhancement (RECIST criteria)(subgroup 2), - CRE1 or CRE2 by CT scanning should show no evidence of pulmonary, osseous, hepatic, or non-regional lymph-node metastases.

### Exclusion criteria

- Patients unfit to receive neo-adjuvant chemotherapy as assessed by Galsky criteria
- Less than four courses of neoadjuvant chemotherapy received,
- Not willing or not fit enough to undergo radical cystectomy
- Concomitant extensive carcinoma in situ at diagnosis
- Poor kidney function with a CrCl (calculated or measured) <60 mL/min
- Concomitant tumors of the upper urinary tract
- Tumors of the urachus
- A known additional malignancy with the exception of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma), cervical cancer in situ that have undergone potentially curative therapy

## Study design

### Design

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|---|---|
| Study type: | Observational non invasive |
| Intervention model: | Other |
| Allocation: | Non controlled trial |
| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 01-02-2020 |
| Enrollment: | 180 |
| Type: | Anticipated |

### IPD sharing statement

**Plan to share IPD:** Undecided

# Ethics review

Positive opinion

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| Date: | 20-05-2020 |
| Application type: | First submission |

# 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 |
|---|---|
| NTR-new | NL8678 |
| Other | METC Amsterdam UMC location VUmc : METC2019.594 - NL70863.029.19 |

# Study results