Clinical-Bladder cancer

Intermediate-term survival of robot-assisted versus open radical cystectomy for muscle-invasive and high-risk non-muscle invasive bladder cancer in The Netherlands

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Received 1 April 2021; received in revised form 31 May 2021; accepted 21 June 2021

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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https://doi.org/10.1016/j.urolonc.2021.06.018
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Abstract

Background: Radical cystectomy with pelvic lymph node dissection is the recommended treatment in non-metastatic muscle-invasive bladder cancer (MIBC). In randomised trials, robot-assisted radical cystectomy (RARC) showed non-inferior short-term oncological outcomes compared with open radical cystectomy (ORC). Data on intermediate and long-term oncological outcomes of RARC are limited.

Objective: To assess the intermediate-term overall survival (OS) and recurrence-free survival (RFS) of patients with MIBC and high-risk non-MIBC (NMIBC) who underwent ORC versus RARC in clinical practice.

Methods and materials: A nationwide retrospective study in 19 Dutch hospitals including patients with MIBC and high-risk NMIBC treated by ORC (n = 1086) or RARC (n = 386) between January 1, 2012 and December 31, 2015. Primary and secondary outcome measures were median OS and RFS, respectively. Survival outcomes were estimated using Kaplan-Meier curves. A multivariable Cox regression model was developed to adjust for possible confounders and to assess prognostic factors for survival including clinical variables, clinical and pathological disease stage, neoadjuvant therapy and surgical margin status.

Results: The median follow-up was 5.1 years (95% confidence interval ([95%CI] 5.0–5.2)). The median OS after ORC was 5.0 years (95%CI 4.3–5.6) versus 5.8 years after RARC (95%CI 5.1–6.5). The median RFS was 3.8 years (95%CI 3.1–4.5) after ORC versus 5.0 years after RARC (95%CI 3.9–6.0). After multivariable adjustment, the hazard ratio for OS was 1.00 (95%CI 0.84–1.20) and for RFS 1.08 (95%CI 0.91–1.27) of ORC versus RARC. Patients who underwent ORC were older, had higher preoperative serum creatinine levels and more advanced clinical and pathological disease stage.

Conclusion: ORC and RARC resulted in similar intermediate-term OS and RFS in a cohort of almost 1500 MIBC and high-risk NMIBC.

Keywords: Bladder cancer; Cystectomy; Muscle invasive; Robot; Survival

Abbreviations: ASA, American Society of Anaesthesiologists classification; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CT, computed tomography; HR, hazard ratio; IQR, interquartile range; MIBC, muscle-invasive bladder cancer; NCR, Netherlands Cancer Registry; NMIBC, non-muscle invasive bladder cancer; ORC, open radical cystectomy; PALGA, Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief; PET, position emission tomography; RARC, robot-assisted radical cystectomy; RCT, randomised controlled trial; STROBE, STrengthening the Reporting of Observational studies in Epidemiology

1. Introduction

Radical cystectomy with pelvic lymph node dissection is the recommended treatment for patients with non-metastatic muscle-invasive bladder cancer (MIBC), or high-risk non-muscle invasive bladder cancer (NMIBC) who are unresponsive to Bacille Calmette-Guérin therapy [1]. The classic surgical approach was an open radical cystectomy (ORC), but in 2006, minimally-invasive surgery by means of either conventional laparoscopy or robot-assisted radical cystectomy (RARC) was introduced [2]. The oncological and non-oncological outcomes of new surgical methods should not be inferior to the current standard of treatment. Monitoring of the outcomes of differing surgical techniques is warranted, as it has previously been shown that patients with early-stage cervical cancer have a higher risk of recurrence and death when robot-assisted radical hysterectomy was performed as an alternative to open surgery [3].

Previous randomised controlled trials (RCTs) that reported on the perioperative outcomes of ORC versus RARC found that both groups had a similar risk of perioperative complications [4–7]. The duration of surgery for RARC was longer, but there was less perioperative blood loss and shorter hospital stay [4–7]. To date, four smaller RCTs that included a total of 829 patients have compared the intermediate-term oncological outcomes of both surgical techniques. These trials, with a median follow-up that varied from 2.0 to 5.5 years, found no difference in overall survival (OS) and recurrence-free survival (RFS) between ORC and RARC. [8–11]. Since these RCTs were not designed for long-term follow-up, the next step is to further investigate intermediate- to long-term oncological outcomes by the analysis of non-randomised studies. Moreover, the RCTs have strict inclusion criteria which do not always correspond to those of ‘real-world’ patients. To date, only two observational studies have included patients from more than two centres, only one of which studied more than 1000 patients [12,13]. This study had a relatively short median follow-up at 27 months and did not report on RFS.

We conducted a ‘real-world’ multicentre study in the Netherlands to assess the intermediate-term OS and RFS of patients with MIBC and high-risk NMIBC who underwent ORC versus RARC.

2. Materials and methods

2.1. Study design

The present study was a retrospective multicentre observational cohort study on patients with non-metastatic MIBC or high-risk NMIBC who underwent ORC or RARC.
as curative treatment between January 2012 and December 2015. To ensure sufficient follow-up for intermediate-term oncological outcomes, the inclusion period was not extended beyond 2015. Eligible patients were identified using the ‘MIBC and cystectomy’ database of the Dutch Association for Urology. This is a prospectively maintained nationwide database in which patients who undergo radical cystectomy for bladder cancer in the Netherlands have been registered since 2012. Of the 47 hospitals in the Netherlands that perform more than five radical cystectomies a year, 37 participated in the registration of the Dutch Association for Urology and were therefore asked to join the present study. There was no selection based on volume or surgical approach. In total, 19 of the 37 hospitals joined the present study, including five academic and 14 general hospitals that conducted between 10 and 61 cystectomies per year. Twelve centres conducted ORC only, two centres conducted RARC only, and five centres conducted both procedures.

The protocol was approved by the medical ethics committee of the Erasmus Medical Centre, Rotterdam (MEC2018-1730), and the need for written informed consent was waived. The strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement and the ROBINS-I tool were used to minimise risk of bias [14,15].

2.2. Patients

Patients with MIBC or high-risk NMIBC, clinical stage T1-T4aN0-1M0, were included from the ‘MIBC and cystectomy’ database. For initial staging of lymph nodes and distant metastases, computed tomography (CT) scanning or position emission tomography (PET)/CT of thorax and abdomen was done in accordance with local hospital protocols. The decision to perform radical surgery was made at multidisciplinary tumour board meetings, and the choice of ORC or RARC followed the regular clinical practice of the local standard of care. After surgery, the course of follow-up was similar in all patients, and in accordance with local protocols based on international guidelines. Follow-up comprised regular CT scanning of thorax and abdomen [1].

2.3. Data collection

At each participating hospital, a local researcher gathered follow-up data and any data missing from the MIBC and cystectomy database from the original patient charts. Pseudo-anonymized data were collected in a Web-based Case Record Form (data management system CASTOR EDC) [16]. Data were collected on age, gender, American Society of Anesthesiologists’ (ASA) classification score, Charlson Comorbidity Index (CCI), body mass index (BMI, kg/m²), preoperative serum haemoglobin (mmol/L) and creatinine concentration (µmol/L), type of neoadjuvant therapy, clinical (cTNM) and pathological (pTNM) stage, estimated perioperative blood loss, duration of surgery (in minutes), surgical margin status, number of reported lymph nodes and lymph node metastases, complications within 90 days of surgery (grade ≥3 according to the Clavien-Dindo system), date of death and date and site of recurrence [17].

Any missing patients or patient data on the cTNM and pTNM disease stage, and the primary outcome (i.e., OS) were supplemented for completeness by data obtained from the Netherlands Cancer Registry (NCR). The NCR is a nationwide network based on a registry of histopathology and cytopathology which includes all patients diagnosed with cancer in the Netherlands (in Dutch: PALGA). Each year, the NCR links up with the Dutch National Municipal Personal Records Database in order to update the vital status of the patient and determine date of death. This allowed the primary outcome of our study to be verified and corrected when necessary.

2.4. Outcome measures

The primary endpoint was the OS defined as the time from the date of radical cystectomy until the date of death, from any cause. If the date of death was unknown, the patient was censored at the last follow-up date. The secondary endpoint was the RFS, defined as the time from the date of radical surgery until the date of disease recurrence. Recurrence was defined as pathologically enlarged lymph nodes, distant metastases or a local pelvic recurrence seen on standard cross-sectional imaging or on histological examination of a diagnostic biopsy of a metastatic lesion.

2.5. Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics version 25. Continuous data were described by the median with interquartile range (IQR). For purposes of postoperative categorical comparisons, the 95% confidence interval (CI) of the proportions was given. Baseline characteristics and clinico-pathological outcomes were compared using the chi-square and Mann-Whitney U-test (2-sided; α 0.05). The median and 5 years OS and RFS with corresponding 95%CI were estimated using Kaplan-Meier survival analyses and patients who were lost to follow-up were censored at the date of last recorded follow-up. Due to the observational design and incomparable patient groups, the Log-rank test was not used to compare survival outcomes.

A multivariable Cox regression model was developed to adjust for possible confounders and to assess prognostic factors for survival such as age at time of surgery, gender, CCI, ASA score, BMI, preoperative haemoglobin and creatinine, cTNM, year of surgery, neoadjuvant therapy, number of severe complications (grade >II), pTNM and surgical margin status. The linearity assumption for continuous variables and the proportional hazard assumption for categorical variables were checked visually. A subgroup analysis was done including only patients with MIBC (cT2-4aN0-
To include all patients in the regression analyses, an imputation procedure of missing values was done using logistic and linear regression models, whereby five data sets were created [18]. The included predictors were age, sex, ASA, CCI, BMI, preoperative creatinine and haemoglobin, year of surgery, neoadjuvant therapy, estimated blood loss and duration of surgery, cTNM, number of severe complications, pTNM and surgical margin status.

3. Results

3.1. Baseline characteristics

In total, 1,472 patients were included: 1,086 patients underwent ORC and 386 underwent RARC. The median follow-up was 5.1 years (95% CI 5.0–5.2). Patients treated with ORC were older (median 69 years, IQR 62–75) than those treated with RARC (median 68 years, IQR 62–74, \( P = 0.07 \)), and had higher serum creatinine level at the time of surgery (median 90 \( \mu \text{mol/L} \), IQR 75–108 versus 85 \( \mu \text{mol/L} \), IQR 73–105, \( P = 0.01 \), for RARC) (Table 1). More patients treated by ORC had clinical lymph node positive disease (9%, 94/1,062) than those treated by RARC (4%, 13/375, \( P < 0.01 \)). Patients treated by ORC had a more adverse pathological tumour stage (>pT2) and lymph node metastases (pN+) than those treated by RARC, i.e., 43% (463/1,083, 95% CI 40–46) versus 33% (128/386, 95% CI 28–38, \( P = 0.02 \)) >pT2 and 24% (255/1,085, 95% CI 21–26) versus 17% (64/386, 95% CI 13–21, \( P = 0.02 \)) pN+, respectively (Table 2).

Table 1
Baseline characteristics of 1,472 patients with muscle-invasive and high-risk non-muscle invasive bladder cancer who were treated with open versus robot-assisted radical cystectomy.

| Characteristics | ORC \( n = 1086 \) | RARC \( n = 386 \) | \( P\text{-value} \) | Missing data, % (\( n \)) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age, years      | 69 (62–75)      | 68 (62–74)      | 0.07\(^a\)       | 0 (1)           |
| Gender, % (\( n \)) | 0.09\(^b\)       |                 |                 |                 |
| Female          | 27 (298)        | 24 (92)         |                 |                 |
| Male            | 73 (788)        | 76 (294)        |                 |                 |
| Charlson comorbidity index | 4 (2–5)       | 4 (2–5)        | 0.81\(^a\)       | 1 (20)          |
| ASA classification, % (\( n \)) | 0.31\(^b\)       |                 |                 |                 |
| I               | 17 (172)        | 18 (70)         |                 |                 |
| II              | 62 (620)        | 64 (245)        |                 |                 |
| III-IV          | 21 (216)        | 18 (68)         |                 |                 |
| Body mass index, kg/m\(^2\) | 26 (23–28)    | 26 (23–29)      | 0.13\(^a\)       | 9 (137)         |
| Haemoglobin, mmol/L | 8.2 (7.1–9.0) | 8.2 (7.3–8.9)  | 0.87\(^a\)       | 2 (26)          |
| Creatinine, \( \mu \text{mol/L} \) | 90 (75–108)  | 85 (73–104)     | 0.01\(^a\)       | 3 (38)          |
| Clinical T stage, % (\( n \)) | 0.07\(^b\)       |                 |                 |                 |
| cTa/T1/Cis      | 19 (204)        | 22 (83)         |                 |                 |
| cT2             | 49 (529)        | 52 (200)        |                 |                 |
| cT3             | 24 (259)        | 19 (74)         |                 |                 |
| cT4             | 7 (75)          | 5 (19)          |                 |                 |
| Clinical N stage, % (\( n \)) | <0.01\(^b\)       |                 |                 |                 |
| cN0             | 91 (968)        | 97 (362)        |                 | 2 (35)          |
| cN1             | 9 (94)          | 4 (13)          |                 |                 |
| Diversion, % (\( n \)) | 0.19\(^b\)       |                 |                 | 0 (6)           |
| Bricker         | 86 (928)        | 82 (313)        |                 |                 |
| Neobladder      | 12 (126)        | 14 (53)         |                 |                 |
| Indiana pouch   | 2 (21)          | 3 (11)          |                 |                 |
| Ureterocutaneostomy | 1 (5)          | 1 (4)           |                 |                 |
| Other           | 1 (5)           | 0               |                 |                 |
| Year of surgery, % (\( n \)) | 0.01\(^b\)       |                 |                 | 0               |
| 2012            | 24 (261)        | 18 (68)         |                 |                 |
| 2013            | 26 (287)        | 22 (83)         |                 |                 |
| 2014            | 25 (275)        | 30 (117)        |                 |                 |
| 2015            | 24 (263)        | 31 (118)        |                 |                 |
| Neoadjuvant therapy, % (\( n \)) | 0.08\(^b\)       |                 |                 | 1 (10)          |
| None            | 78 (843)        | 73 (277)        |                 |                 |
| Chemotherapy    | 21 (222)        | 26 (99)         |                 |                 |
| Radiotherapy    | 1 (10)          | 0 (1)           |                 |                 |
| Other           | 1 (8)           | 1 (2)           |                 |                 |

ASA = American Society of Anesthesiologists; ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy

Continuous data are presented as median (interquartile range) and categorical data as percentage (frequency).

\(^a\)Mann-Whitney Test

\(^b\)Chi-squared statistic
3.2. Survival outcomes

The median OS of patients treated by ORC versus RARC was 5.0 (95%CI 4.3–5.6) versus 5.8 years (95%CI 5.1–6.5), and the 5–years OS was 50% (95%CI 47–53) versus 58% (95%CI 52–63) (Fig. 1). After multivariable adjustment, the hazard ratio (HR) of ORC versus RARC for OS was 1.00 (95%CI at 0.84–1.20, \(P = 0.96\)) (Table 3). Higher age and CCI >5, preoperative anaemia (defined as haemoglobin <7.5 mmol/L for females and <8.5 mmol/L for males), severe complications, >pT2 and >pN0 disease stage and positive surgical margins were associated with worse OS.

The median RFS of patients treated by ORC versus RARC was 3.8 years (95%CI 3.1–4.5) versus 5.0 years (95%CI 3.9–6.0) and the 5-years RFS was 44% (95%CI 41–47) versus 50% (95%CI 45–55) (Fig. 2). After multivariable adjustment, the HR for RFS of ORC versus RARC was 1.08 (95%CI at 0.91–1.27, \(P = 0.38\)) (Table 3). Higher age and CCI >5, preoperative anaemia, severe complications, >pT2 and >pN0 disease stage and positive surgical margins were associated with worse RFS. After ORC, distant recurrences were observed more frequently (28%, 289/1,051) than after RARC (22%, 85/384, \(P = 0.01\)) (Table 4). No

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**Table 2**

Pathological outcomes of 1,472 patients with muscle-invasive and high-risk non-muscle invasive bladder cancer who were treated with open versus robot-assisted radical cystectomy.

| Pathological T stage, % (n) | ORC  
|----------------------------| n = 1086 | RARC  
|----------------------------| n = 386 | \(P\)-value | Missing data, % (n) |
| pT0 | 17 (184) | 22 (84) | 0.02b | 0 (3) |
| pTa/T1/Cis | 20 (215) | 22 (85) | 0.02b | 0 (3) |
| pT2 | 20 (221) | 23 (89) | 0.02b | 0 (3) |
| pT3 | 31 (333)c | 25 (96)d | 0.02b | 0 (3) |
| pT4 | 12 (130)e | 8 (32)f | 0.02b | 0 (3) |
| Pathological N stage, % (n) | ORC  
|----------------------------| n = 1086 | RARC  
|----------------------------| n = 386 | \(P\)-value | Missing data, % (n) |
| pN0 | 74 (802) | 81 (313) | 0.06b | 1 (19) |
| pN+ | 23 (255) | 17 (64) | 0.06b | 1 (19) |
| PNx | 3 (28) | 2 (9) | 0.06b | 1 (19) |
| Pathological M stage, % (n) | ORC  
|----------------------------| n = 1086 | RARC  
|----------------------------| n = 386 | \(P\)-value | Missing data, % (n) |
| PMx | 100 (1086) | 100 (386) | 0.06b | 1 (19) |
| Histology, % (n) | ORC  
|----------------------------| n = 1086 | RARC  
|----------------------------| n = 386 | \(P\)-value | Missing data, % (n) |
| Urothelial carcinoma | 84 (899) | 88 (334) | 0.06b | 1 (19) |
| Non-urothelial carcinoma | 16 (174) | 12 (46) | 0.06b | 1 (19) |
| Lymph nodes harvested | 15 (10–21) | 15 (10–19) | 0.06b | 1 (19) |
| Positive lymph nodes | 2 (1–3) | 2 (1–3) | 0.06b | 1 (19) |
| Surgical margin status, % (n) | ORC  
|----------------------------| n = 1086 | RARC  
|----------------------------| n = 386 | \(P\)-value | Missing data, % (n) |
| Negative | 89 (935) | 92 (351) | 0.06b | 1 (19) |
| Positive | 11 (120) | 8 (30) | 0.06b | 1 (19) |

ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

Continuous data are presented as median (interquartile range) and categorical data as percentage (frequency).

\( ^{a} \)Mann-Whitney Test

\( ^{b} \)Chi-squared statistic

\( ^{c} \)of which \( pT3a \ n = 181 \) and \( pT3b \ n = 152 \)

\( ^{d} \)of which \( pT3a \ n = 53 \) and \( pT3b \ n = 43 \)

\( ^{e} \)of which \( pT4a \ n = 105 \) and \( pT4b \ n = 25 \)

\( ^{f} \)of which \( pT4a \ n = 27 \) and \( pT4b \ n = 5 \)
Sensitivity analyses of the multivariable regression in a subgroup of 1,156 patients with MIBC showed no benefit of OS and RFS after ORC (n = 863) versus RARC (n = 293) (Supplementary Table 1).

### 4. Discussion

This is the largest multicentre series to date to report on the intermediate-term survival outcome of ORC versus RARC in a cohort of almost 1,500 patients with non-metastatic MIBC or high-risk NMIBC. The intermediate-term OS and RFS were similar for ORC versus RARC after multivariable adjustments for possible confounders.

In the present study, the 5-years OS of 58% (95% CI 52–63%) and 5-years RFS of 50% (95% CI 45–55%) after RARC are in line with findings from previous studies, ranging from 59 to 65% and 54 to 71%, respectively [8,19,20]. In contrast, the 5-years OS of 50% (95% CI 47–53%) and RFS of 44% (95% CI 41–47%) after ORC were worse than previously described, ranging from 55% to 58% and 57% to 65%, respectively [8,19,20]. This is probably explained by the inclusion of differing patient groups. Our study

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**Table 3**

Multivariable Cox regression models to assess the association between type of intervention (open versus robot-assisted radical cystectomy) and overall survival or recurrence-free survival and to assess possible predictors for survival

|                               | Overall survival | Recurrence-free survival |
|-------------------------------|-----------------|--------------------------|
|                               | HR 95% CI       | P-value                   | HR 95% CI       | P-value                   |
| Age per 10 years              | 1.17 1.07–1.29  | <0.01                    | 1.12 1.03–1.23  | <0.01                    |
| Female sex                    | 1.15 0.97–1.36  | 0.11                     | 1.08 0.92–1.27  | 0.37                     |
| Charlson comorbidity Index    |                 |                          |                |                          |
| <5               | Reference       |                          | Reference       |                          |
| 5                | 1.22 0.97–1.53  | 0.11                     | 1.13 0.91–1.41  | 0.25                     |
| >5               | 1.51 1.22–1.87  | <0.01                    | 1.45 1.18–1.77  | <0.01                    |
| ASA classification           |                 |                          |                |                          |
| I                | Reference       |                          | Reference       |                          |
| II               | 0.94 0.75–1.17  | 0.57                     | 1.00 0.81–1.24  | 0.99                     |
| III-IV           | 0.99 0.75–1.32  | 0.99                     | 1.00 0.76–1.32  | 0.99                     |
| Body mass index per kg/m²    | 0.99 0.96–1.01  | 0.16                     | 1.00 0.98–1.02  | 0.79                     |
| Anaemia            | 1.37 1.15–1.63  | <0.01                    | 1.31 1.12–1.54  | <0.01                    |
| Creatinine per 10 μmol/l    | 1.01 0.99–1.02  | 0.35                     | 1.00 0.99–1.02  | 0.67                     |
| Clinical T stage<sup>c</sup> | Reference       |                          | Reference       |                          |
| cTa/T1/Cis         | 1.24 0.98–1.58  | 0.07                     | 1.10 0.89–1.37  | 0.36                     |
| cT2–cT4           | 1.26 0.94–1.69  | 0.13                     | 1.12 0.84–1.48  | 0.45                     |
| Clinical N+ stage   |                 |                          |                |                          |
| 2012              | 0.90 0.72–1.13  | 0.36                     | 0.92 0.74–1.13  | 0.43                     |
| 2013              | 1.02 0.82–1.27  | 0.83                     | 1.03 0.85–1.27  | 0.75                     |
| 2014              | 1.02 0.82–1.28  | 0.83                     | 1.02 0.83–1.25  | 0.89                     |
| 2015              | Reference       |                          | Reference       |                          |
| Neoadjuvant therapy<sup>d</sup> | Reference       |                          | Reference       |                          |
| None              | 0.85 0.68–1.07  | 0.16                     | 0.87 0.70–1.08  | 0.21                     |
| Chemotherapy or Radiotherapy|                 |                          |                |                          |
| 1<sup>†</sup> | Reference       |                          | Reference       |                          |
| Severe complications<sup>d</sup> | Reference       |                          | Reference       |                          |
| None              | 1.76 1.50–2.07  | <0.01                    | 1.64 1.41–1.91  | <0.01                    |
| Pathological T stage<sup>d</sup> | Reference       |                          | Reference       |                          |
| pT0–pT2          | 2.36 1.98–2.80  | <0.01                    | 2.32 1.97–2.74  | <0.01                    |
| pT3–pT4          | 1.82 1.53–2.17  | <0.01                    | 1.96 1.66–2.31  | <0.01                    |
| Pathological N+ stage | 1.69 1.37–2.09  | <0.01                    | 1.67 1.36–2.04  | <0.01                    |
| Positive surgical margin status | 1.00 0.84–1.20  | 0.96                     | 1.08 0.91–1.27  | 0.38                     |

ASA = American Society of Anesthesiologists; CI = confidence interval; HR = hazard ratio; ORC = open radical cystectomy.

<sup>a</sup>The model included 1472 patients and 718 events.

<sup>b</sup>The model included 1472 patients and 812 events.

<sup>c</sup>Haemoglobin was categorised into anaemia because of non-linearity. Anaemia was defined as haemoglobin < 7.5 mmol/L for females and < 8.5 mmol/L for males.

<sup>d</sup>Clinical T stage, neoadjuvant therapy, number of severe complications and pathological T stage were dichotomised after check for proportional hazards assumption.

<sup>†</sup>Check for proportional hazards assumption showed a higher hazard for patients with clinical N+ stage disappeared after approximately 6 years

<sup>f</sup>Check for proportional hazards assumption showed a lower hazard for patients with neoadjuvant therapy appeared after approximately 2 years
included more cN1 patients, 9% in the ORC group vs. 0% in previous studies. In the only study that also included cN1 patients, about 60% were treated with NAC compared with 25% in our study [20].

Patients treated by ORC were older than those treated by RARC, they had higher preoperative serum creatinine levels and were at a more advanced clinical disease stage. This probably reflects a selection bias towards patients with favourable preoperative clinical characteristics for RARC. Interestingly, this was not reflected in the comorbidity and ASA classification rates as these were similar in both cohorts.

Pathological tumour stage, nodal positivity and positive surgical margin rate have been shown to serve as a surrogate for survival [21,22]. As our results show, patients treated by ORC had statistically significant higher pathological disease stage, 43% (95% CI 40–46) pT3-4 patients versus 33% (95% CI 28–38) in the RARC group. It is probable that this contributed to the slightly higher rate of positive surgical margin of 11% (95% CI 10–13) seen after ORC vs. 8% (95% CI 5–11) after RARC. An exploratory survival analysis of ORC vs. RARC in 427 patients with extravesical disease (cT3-4) showed no difference in OS and RFS between the interventions (data not shown). Therefore, there is no clear preference for surgical technique in patients with clinical locally advanced disease.

In an unadjusted analysis, distant recurrences were observed significantly more frequently after ORC, probably following the imbalance of pTN-stage and longer follow-up in ORC patients. However, similar to previous studies, the local recurrence rate in our study was similar after ORC and RARC [9,20]. This should ease concerns about a higher local recurrence rate after RARC [10].

According to the NCR, between 2012 and 2015 approximately 3,000 patients with MIBC or high-risk NMIBC underwent ORC or RARC in the Netherlands, almost 1,500 of whom were included in the present study. This cohort of 3,000 also includes patients treated with chemo-radiotherapy or palliative cystectomy. Our study is a cooperation of five academic and 14 general hospitals out of a total of 47 Dutch hospitals. Overall, we estimate our study includes at least half of eligible Dutch patients. Moreover, no inclusion criteria for patients or hospitals were used thereby representing clinical practice.

The present study is limited by its observational and retrospective nature which have led to an imbalance in prognostic factors. Although we used multivariable adjustment to reduce confounders between surgical strategies, the risk of residual confounding and unobserved confounders remains. A propensity score matched analysis to further reduce imbalanced covariates was not performed. Main reason for this was that propensity score matching leads to loss of information by limiting the analysis to only a subgroup of patients rather than reflecting routine clinical practice. No future RCTs on the comparison of ORC vs. RARC for intermediate- to long-term oncological outcomes are expected. This justifies the comparison of both therapies in large observational series such as our “real-world” study. Data on adjuvant therapy were not retrieved, but since it is

![Fig. 2. Kaplan-Meier estimates of the recurrence-free survival in 1,472 non-metastatic muscle-invasive bladder cancer and high-risk non-muscle invasive bladder cancer patients who underwent radical cystectomy. Red line indicates robot-assisted radical cystectomy (RARC) and blue line indicates open radical cystectomy (ORC). (Color version of figure is available online.)](image-url)

Table 4
Sites of recurrence in patients with muscle-invasive and high-risk non-muscle invasive bladder cancer after open versus robot-assisted radical cystectomy.

| Site of recurrence, % (n) | ORC n = 1051 | RARC n = 384 | P-value |
|--------------------------|--------------|--------------|---------|
| Loco-regional            |              |              |         |
| Pelvic lymph nodes       | 18 (193)     | 17 (65)      | 0.53    |
| Pelvic soft tissue       | 7 (74)       | 5 (18)       |         |
| Rectum                   | 1 (14)       | 1 (2)        |         |
| Upper urinary tract      | 2 (19)       | 3 (12)       |         |
| Urethra                  | 2 (20)       | 1 (5)        |         |
| Distant                  |              |              |         |
| Abdominal wall           | 28 (289)     | 22 (85)      | 0.04    |
| Intestines               | 1 (5)        | 2 (8)        |         |
| Peritoneum               | 1 (12)       | 1 (4)        |         |
| Intra-abdominal soft tissue | 2 (16) | 3 (10)       |         |
| Adrenal                  | 1 (9)        | 1 (3)        |         |
| Bone                     | 9 (101)      | 5 (21)       |         |
| Extra pelvic lymph nodes | 8 (89)       | 7 (28)       |         |
| Liver                    | 6 (63)       | 5 (18)       |         |
| Lung                     | 8 (87)       | 7 (28)       |         |
| Extra abdominal soft tissue | 1 (8) | 1 (3)        |         |
| Other                    | 1 (12)       | 1 (4)        |         |

ORC = open radical cystectomy; RARC = robot-assisted radical cystectomy.

*Missing site of recurrence n = 37/1472 (3%). Categorical data as a percentage (frequency).

Note: several patients had more than one site of disease recurrence
unlikely that the surgical technique itself affected the rate and type of adjuvant therapy, we consider the lack of these data had little influence on our primary outcome. In addition, data on intracorporeal versus extracorporeal urinary diversion and hydronephrosis were not retrieved and imaging or biopsies at time of recurrence were not centrally revised. Seven of 19 hospitals conducted RARC, and it is quite likely that at the time some surgeons were still following the learning curve for this procedure. If this was indeed the case, more recent series might show improved survival outcomes.

The present study has little missing data, which was accomplished by supplementing the data from the database of the Dutch Association of Urology with data from both the local patient report and the NCR database. In addition, the accuracy of the primary endpoint was verified by the use of municipal registers from the NCR database.

5. Conclusion

We found similar intermediate-term OS and RFS in a cohort of 1,472 non-metastatic MIBC and high-risk NMIBC patients who underwent RARC or ORC after a median follow-up of more than 5 years and correction for confounding variables. Patients who underwent ORC were older, had higher preoperative serum creatinine levels and more advanced clinical and pathological disease stage, which reflects the selection of patients with more favourable prognostic factors for RARC in clinical practice.

Conflict of interest

All authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.06.018.

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