Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial

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Summary

Background Radical cystectomy is the surgical standard for invasive bladder cancer. Robot-assisted cystectomy has been proposed to provide similar oncological outcomes with lower morbidity. We aimed to compare progression-free survival in patients with bladder cancer treated with open cystectomy and robot-assisted cystectomy.

Methods The RAZOR study is a randomised, open-label, non-inferiority, phase 3 trial done in 15 medical centres in the USA. Eligible participants (aged ≥18 years) had biopsy-proven clinical stage T1–T4, N0–N1, M0 bladder cancer or refractory carcinoma in situ. Individuals who had previously had open abdominal or pelvic surgery, or who had any pre-existing health conditions that would preclude safe initiation or maintenance of pneumoperitoneum were excluded. Patients were centrally assigned (1:1) via a web-based system, with block randomisation by institution, stratified by type of urinary diversion, clinical T stage, and Eastern Cooperative Oncology Group performance status, to receive robot-assisted radical cystectomy or open radical cystectomy with extracorporeal urinary diversion. Treatment allocation was only masked from pathologists. The primary endpoint was 2-year progression-free survival, with non-inferiority established if the lower bound of the one-sided 97·5% CI for the treatment difference (robotic cystectomy minus open cystectomy) was greater than –15 percentage points. The primary analysis was done in the per-protocol population. Safety was assessed in the same population. This trial is registered with ClinicalTrials.gov, number NCT01157676.

Findings Between July 1, 2011, and Nov 18, 2014, 350 participants were randomly assigned to treatment. The intended treatment was robotic cystectomy in 176 patients and open cystectomy in 174 patients. 17 (10%) of 176 patients in the robotic cystectomy group did not have surgery and nine (5%) patients had a different surgery to that they were assigned. 21 (12%) of 174 patients in the open cystectomy group did not have surgery and one (1%) patient had robotic cystectomy instead of open cystectomy. Thus, 302 patients (150 in the robotic cystectomy group and 152 in the open cystectomy group) were included in the per-protocol analysis set. 2-year progression-free survival was 72·3% (95% CI 64·3 to 78·8) in the robotic cystectomy group and 71·6% (95% CI 63·6 to 78·2) in the open cystectomy group (difference 0·7%, 95% CI –9·6% to 10·9%; $p_{non\text{-}inferiority}$=0·001), indicating non-inferiority of robotic cystectomy. Adverse events occurred in 101 (67%) of 150 patients in the robotic cystectomy group and 105 (69%) of 152 patients in the open cystectomy group. The most common adverse events were urinary tract infection (53 [35%] in the robotic cystectomy group *vs* 39 [26%] in the open cystectomy group) and postoperative ileus (33 [22%] in the robotic cystectomy group *vs* 31 [20%] in the open cystectomy group).

Interpretation In patients with bladder cancer, robotic cystectomy was non-inferior to open cystectomy for 2-year progression-free survival. Increased adoption of robotic surgery in clinical practice should lead to future randomised trials to assess the true value of this surgical approach in patients with other cancer types.

Funding National Institutes of Health National Cancer Institute.

Introduction

Robotic surgery has been proposed to improve surgical outcomes by maintaining cancer control while decreasing pain and complications. Following the approval of the robotic platform in 2000, this approach was rapidly adopted across many surgical disciplines, and has been used for around 4 million surgical procedures worldwide.[1] In 2016, 3919 robotic surgical systems were used for 753 000 procedures globally.[1]

The Idea, Development, Exploration, Assessment, and Long-term Follow-up (IDEAL) initiative has recommended an incremental evidence-based assessment of surgical

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Research in context

Evidence before this study

Surgical robotic technology has become available for the management of patients globally, however, high level evidence to support the benefit of such approaches is scarce. A small number of single-centre randomised trials assessing robotic technology have been done with primary endpoints focused on perioperative recovery. Multicentre randomised trials comparing robotic surgery with open surgery to assess oncological endpoints have not yet been reported. Despite the lack of high level evidence, a substantial proportion of urological cancer surgeries are robot-assisted.

We searched PubMed for studies published between Jan 1, 2011, and Aug 10, 2017, without date or language restrictions, using the search terms "robotic surgery", "randomised trial", "robot-assisted radical cystectomy", "robotic radical cystectomy", "minimally invasive radical cystectomy", and "open versus robotic radical cystectomy". Numerous retrospective studies have shown that robot-assisted radical cystectomy is technically feasible and has the potential to reduce blood loss and complication rates. Two single-centre pilot randomised studies comparing open cystectomy with robotic cystectomy found no difference between the procedures in surgical surrogates of oncological efficacy, such as positive margins and lymph node yield, and no difference in complication rates, but better perioperative outcomes, including reduced blood loss and length of hospital stay, in the robotic group than the open cystectomy group. A subsequent single-centre randomised trial and retrospective studies reported similar results. We found no large multicentre prospective trials of robotic cystectomy for bladder cancer and no multicentre trials comparing open surgery with robotic surgery to assess survival endpoints at any organ site.

Added value of this study

This is the first phase 3 trial comparing robot-assisted cystectomy with open cystectomy for any urological cancer. We found that 2-year progression-free survival in patients with bladder cancer who had robotic cystectomy was non-inferior to that of patients who had open cystectomy. Estimated blood loss, blood transfusion rates, and median length of hospital stay were also significantly lower in the robotic cystectomy group than the open cystectomy group. However, no significant differences were identified between groups in major complications (Clavien-Dindo grade ≥3), lymph node yield, positive surgical margins, and patient-reported health related quality-of-life (QoL) outcomes. Duration of surgery was significantly longer for robotic surgery than open surgery.

Our data suggest that robotic cystectomy is non-inferior to open cystectomy with regard to oncological outcomes and reinforces the fact that such trials are possible and should be attempted across other surgical specialties.

Implications of all the available evidence

This trial provides the first multicentre randomised evidence of the oncological efficacy of robotic cystectomy. In the setting of previous studies, robotic cystectomy did not compromise oncological outcomes compared with open cystectomy. Our results showed that robotic cystectomy is associated with an improvement in perioperative parameters, such as blood loss and length of stay, without significant differences in complication rates and patient-reported QoL outcomes. These findings provide high level evidence to inform discussion between patients and their physicians regarding the benefits and risks of various approaches for a complex and often morbid surgery, such as radical cystectomy. Our results also underscore the need for further high-quality trials to assess surgical innovation before this surgical technique is widely adopted in clinical practice.

innovation, culminating in randomised trials. The recommendations call for sequential reporting of cases during early development, and later collaborative prospective cohort studies to help reach consensus on randomised trial design.[2] To the best of our knowledge, no multicentre trials have been done to assess whether robot-assisted surgery is comparable to open surgery for cancer control, using survival endpoints such as progression-free survival.

In 2018, approximately 81 190 patients will be diagnosed with bladder cancer and 17 240 deaths will be attributed to the disease.[3] Radical cystectomy with pelvic lymphadenectomy and urinary diversion is the standard surgical treatment for invasive bladder cancer. Open cystectomy is a complex surgical procedure, with a risk of substantial blood loss, perioperative complications, and mortality.[4] Laparoscopic cystectomy is a minimally invasive approach that was initially developed to reduce the complications of open surgery. However, the procedure is associated with an extensive learning curve and thus, it has not been widely adopted in clinical practice. Robot-assisted radical cystectomy has advantages compared with traditional laparoscopy, including a magnified view and mechanical wrists, which enable more bend and rotation than the human hand.[5] The procedure represents a reproducible minimally invasive alternative to open surgery, but oncological outcomes have not been compared directly. Potential concerns about robotic cystectomy include the lack of tactile feedback, which is considered to be important for complete resection of locally advanced disease, and possible recurrence of cancer in uncommon locations (eg, peritoneal carcinomatosis).[5,6] Concerns have also been raised about the learning curve and cost of robotic surgery.[5,6]

The Randomised Open versus Robotic Cystectomy (RAZOR) trial was designed to investigate whether

robot-assisted radical cystectomy was non-inferior to open radical cystectomy for the treatment of bladder cancer.

Methods

Study design

The RAZOR study is a multicentre, open-label, randomised, phase 3, non-inferiority trial comparing robot-assisted laparoscopic radical cystectomy (robotic cystectomy) with open radical cystectomy for the treatment of bladder cancer, and was done at 15 medical centres in the USA. Institutional review board approval was obtained at each site. The study protocol is available in the appendix (pp 15–34).

Patients

Patients were eligible if they were aged 18 years or older and had biopsy-proven clinical stage T1–T4, N0–N1, M0 bladder cancer or refractory carcinoma in situ. Patients who had previously had open abdominal or pelvic surgery or who had any pre-existing health conditions that would preclude safe initiation or maintenance of pneumoperitoneum were excluded. Pregnant women were also excluded. Written informed consent was obtained from all patients

Randomisation and masking

By use of a dynamic balancing algorithm, patients were centrally randomly assigned (1:1) via a web-based system, to receive open cystectomy or robotic cystectomy. Using each institution as a block, the dynamic allocation procedure allocated an approximately equal number of patients to treatment groups to minimise imbalance between groups, stratified by type of urinary diversion (incontinent or continent), clinical T stage (carcinoma in situ, T1–T2, or T3–T4), and Eastern Cooperative Oncology Group (ECOG) performance status (0–1, or ≥2). On accrual a hierarchical decision-rule was applied, and the allocation was deterministic if certain predefined limits were exceeded, and random otherwise.

Treatment allocation was only masked from pathologists, who analysed the cystectomy specimens.

Procedures

Pathological review was done at each institution to determine whether patients had bladder cancer and to stage and grade the cystectomy specimens. Robotic and open cystectomies were done at all participating institutions. Each surgeon was required to have done at least ten radical cystectomies (open or robotic approaches) in the year before the study. No accepted or validated definition of the learning curve for open or robotic radical cystectomy exists. Radical cystectomy is a core urology expertise learnt during residency, which is enhanced during urological oncology fellowship. All participating surgeons were either fellowship-trained or had a focused practice in bladder cancer.

Urinary diversion was done extracorporeally according to patient and surgeon preference. Details of surgical template, lymphadenectomy, and pathological evaluation have been described previously (appendix pp 5–7).[7] Pathological reports were audited by each institution before final analyses. Pathology data, including margin status and T stage, were reviewed by primary investigators at each site. Extent of pelvic lymph node dissection (standard or extended) and use of chemotherapy was based on institutional preference. Perioperative morbidity was assessed using the modified Clavien-Dindo classification system for complications within 90 days of surgery (appendix pp 8, 9). Perioperative management was according to institutional protocol.

See Online for appendix

Patients were followed up for bladder cancer progression or death from any cause at 4–6 weeks, then every 3–6 months for a minimum of 2 years after cystectomy. Minimum 2-year follow-up was completed on Jan 31, 2017. Chest, abdomen, and pelvic imaging was done at baseline and at least annually to assess recurrence.[7] Patients known to be alive and progression free were censored at last contact. Serum haemoglobin, creatinine, and albumin concentrations were measured at baseline and postoperatively at 4–6 weeks, and months 3, 6, 12, 24, and 36. Quality-of-life (QoL) outcomes were assessed at baseline and 3 months and 6 months after surgery using Short Form-8 and Functional Assessment of Cancer Therapy (FACT)-Vanderbilt Cystectomy Index (VCI) questionnaires. The FACT-VCI is composed of the FACT-General form, which includes four domains (physical, social, emotional, and functional wellbeing) and 17 questions assessing bladder cancer-specific QoL, which are scored on a 5-point Likert scale, with a higher score indicating better QoL. Hand grip strength was assessed at baseline, 4–6 weeks, 3 months and 6 months. Overall survival was assessed at 4–6 weeks, and months 3, 6, 12, 24, and 36. Data were submitted electronically to Cancer Research and Biostatistics (Seattle, WA, USA) for analyses.

Outcomes

The primary endpoint was progression-free survival at 2 years after surgery. Disease progression was determined on the basis of radiographical or pathological evidence of disease, or death from disease according to Response Evaluation Criteria in Solid Tumours criteria version 1.1. Any documented recurrence, or death from other causes was also considered progression. The secondary endpoints were blood loss, the proportion of patients requiring blood transfusion, surgical margin status, number of lymph nodes resected, operating time, length of hospital stay, surgical complications at 90 days, change in health-related QoL outcomes at 3 and 6 months. Change in baseline serum haemoglobin, creatinine, and albumin concentrations at 4–6 weeks, and at 3, 6, 12, 24, and 36 months, intraoperative fluid requirements, and

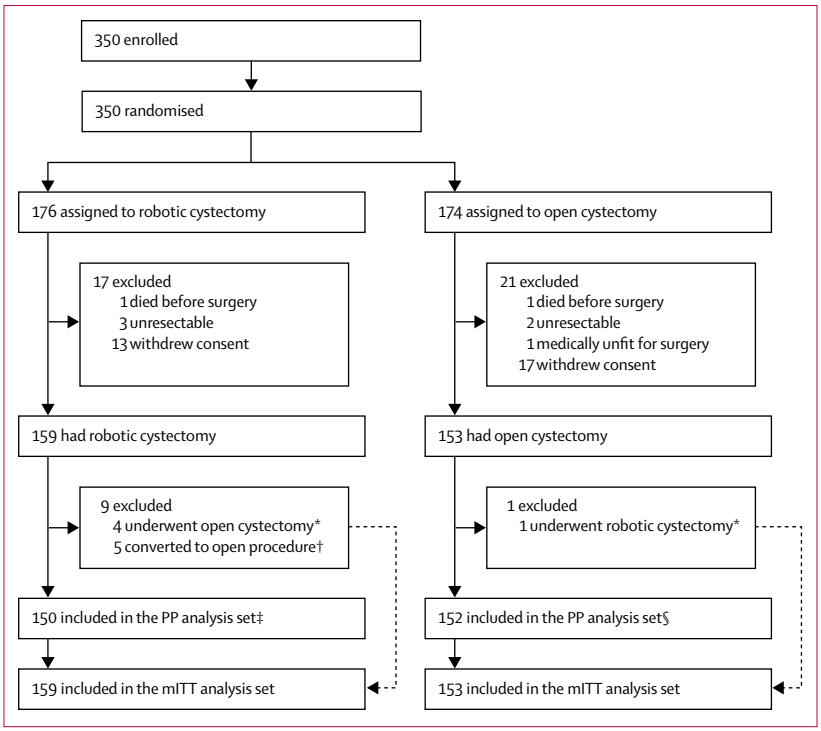


Figure 1: **Trial profile**
The number of patients assessed for eligibility was not available. PP=per-protocol. mITT=modified intention-to-treat. *Patients received the wrong procedure due to screening failure (n=2), failure to notify surgeon of randomisation (n=2), and unknown reasons (n=1). †Conversions were due to locally advanced disease (n=2), inadequate visualisation (n=1), inability to tolerate steep Trendelenburg position (n=1), and incidental detection of coexisting large colonic mass (n=1). ‡During the 2-year follow-up period, data for ten patients were censored, including one patient who was lost to follow-up. §During the 2-year follow-up period, data for 14 patients were censored, including six patients who were lost to follow-up.

	Robotic cystectomy (n=150)	Open cystectomy (n=152)
Median age, years (range)	70 (43–90)	67 (37–85)
Sex		
Men	126 (84%)	128 (84%)
Women	24 (16%)	24 (16%)
Body-mass index (kg/m²)		
Median (IQR)	27·8 (25·0–30·8)	28·2 (24·9–31·7)
<25	38 (25%)	39 (26%)
25–29·9	60 (40%)	64 (42%)
≥30	52 (35%)	49 (32%)
ECOG performance status		
0	117 (78%)	109 (72%)
1	29 (19%)	39 (26%)
2–3	4 (3%)	4 (3%)
Clinical and TURBT stage*		
Tis	6 (4%)	6 (4%)
Ta	1 (1%)	4 (3%)
T1	41 (27%)	41 (27%)
T2	82 (55%)	81 (53%)
T3	16 (11%)	16 (11%)
T4	4 (3%)	4 (3%)
Perioperative chemotherapy	62 (41%)	70 (46%)
Neoadjuvant chemotherapy†	41 (27%)	55 (36%)
Adjuvant chemotherapy†	25 (17%)	17 (11%)
Urinary diversion procedure‡		
Neobladder	36 (24%)	30 (20%)
Ileal conduit	113 (75%)	122 (80%)
Continent cutaneous reservoir	1 (1%)	..
Baseline haemoglobin (g/dL), mean (SD)	13·05 (1·87)	12·81 (1·87)

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. TURBT=transurethral resection of bladder tumour. *Staging according to American Joint Committee on Cancer staging for bladder cancer 7th edition.[15] †Data on chemotherapy use and type of chemotherapy were not available for two patients in the open cystectomy group, and data on chemotherapy type was not available for one patient in the robotic cystectomy group. Five patients in the robotic cystectomy group and two in the open cystectomy group received neoadjuvant and adjuvant chemotherapy. ‡Three patients in the robotic cystectomy group had ileal conduit instead of the planned neobladder urinary diversion, one patient had neobladder instead of ileal conduit urinary diversion, and one patient had continent cutaneous reservoir instead of the planned ileal conduit urinary diversion. Nine patients in the open cystectomy group had ileal conduit instead of the planned neobladder urinary diversion, and one patient had neobladder instead of the planned ileal conduit urinary diversion.

Table 1: **Baseline patient characteristics of the per-protocol population**

analgesic requirements were also assessed as secondary outcomes and will be reported elsewhere.

Prespecified exploratory endpoints were overall survival, activities and instrumental activities of daily living scores, hand grip strength, and timed up and go walking test outcomes, assessed at 4–6 weeks, 3 months, and 6 months after surgery, which will be reported elsewhere.

All complications and adverse events were assessed by site investigators using the modified Clavien-Dindo classification system.

Statistical analysis

We selected a non-inferiority margin of –15 percentage points because it was considered to be clinically significant when a procedure was thought to decrease perioperative morbidity. This margin was chosen on the basis of data available at the time of protocol development, and consensus among trial investigators who are specialists in this field. Specifically, we reviewed chemoradiation therapy as an alternative to the gold standard of open radical cystectomy. The proposed benefits of the robotic approach in terms of decreased perioperative morbidity, and shorter time to receive adjuvant chemotherapy were considered a reasonable trade-off with a potential margin of 15% for 2-year progression.[8–10] Although no randomised data for oncological endpoints comparing the robotic and open approaches for any organ were available when designing our study, we were guided by previous trials[11,12] in colon and rectal cancer comparing laparoscopic with open surgery in which a non-inferiority margin of 15% for progression-free survival had been used.

	Robotic cystectomy	Open cystectomy	Difference (95% CI)	p value*
Per-protocol analysis set				
Patients with disease progression within 2 years of surgery	41/150 (27%)	42/152 (28%)	..	..
2-year progression-free survival (95% CI)	72·3% (64·3 to 78·8)	71·6% (63·6 to 78·2)	0·7% (–9·6 to 10·9)	0·001
Patients with disease progression (total events)†	49/150 (33%)	50/152 (33%)	..	..
Modified intention-to-treat analysis set				
Patients with disease progression within 2 years of surgery	43/159 (27%)	42/153 (27%)	..	..
2-year progression-free survival (95% CI)	72·3% (64·5 to 78·6)	71·8% (63·8 to 78·3)	0·5% (–9·7 to 10·6)	0·001
Patients with disease progression (total events)†	52/159 (33%)	50/153 (33%)	..	..

Data are % (95% CI) or n/N (%), unless otherwise specified. *One-sided p value for non-inferiority. †Total events that had occurred by the data cutoff.

Table 2: **Analysis of progression-free survival**

On the basis of a previous study[13] in which 71% of patients who had open cystectomy were progression-free at 2 years, a sample size of 144 patients per treatment group would achieve 80% power to detect non-inferiority at a one-sided α of 0·025. Additionally, non-inferiority would be established if the lower bound of the one-sided 97·5% CI for the treatment difference (robotic cystectomy minus open cystectomy) was greater than –15 percentage points. Assuming a dropout rate of 10–15%, accrual was increased to 175 patients in each group. Our study was adequately powered to detect significant differences in estimated blood loss, blood transfusion rate, and length of stay as described previously.[7]

Progression-free survival was analysed using the Kaplan-Meier method, with groups compared using the log-rank test. The non-inferiority test and the estimated CI for the difference in 2-year progression-free survival between the treatment groups were derived using methods accounting for censored observations.

The primary endpoint was analysed in the per-protocol population, which included all patients who had the surgery they were assigned to receive.[14] A sensitivity analysis of the primary endpoint was repeated using the modified intention-to-treat population, which included all patients who were randomly assigned and received surgery.

All secondary endpoints were analysed in the per-protocol population. Differences between treatment groups were assessed using the Student's *t* test or Wilcoxon rank sum test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables. Associations between groups and categorical outcomes were reported as estimated difference with accompanying 95% CIs.

For each QoL endpoint, estimated mean scores were obtained for each treatment group and timepoint, adjusted for key covariates from mixed modelling repeated measures analysis, using maximum likelihood estimation and assuming any missing data are missing at random. The fitted mixed effect model included timepoint, treatment group, time × treatment group interaction, age (continuous), sex, body-mass index (<25, 25–29·9, ≥30 kg/m²), ECOG performance status (0, 1+), T-stage (Ta, Tis, T1–T2 *vs* T3–T4), perioperative chemotherapy (no, yes), and urinary diversion procedure (neobladder *vs* other) as fixed-effects. Additionally, the model included patient-level intercepts as random effects, with patients nested within site, and a heterogeneous autoregressive covariance matrix to account for the correlated data structure. The interaction term was included in models regardless of its significance to allow assessment of prespecified estimated mean comparisons of interest (ie, group comparison at each timepoint and comparisons at each timepoint relative to baseline within each group). For each QoL outcome we reported estimated mean scores with corresponding 95% CIs, and p values adjusted for multiple comparisons among estimated means using Bonferroni's method. SAS statistical software (version 9.4) was used for all analyses. The study was overseen by a data and safety monitoring committee.

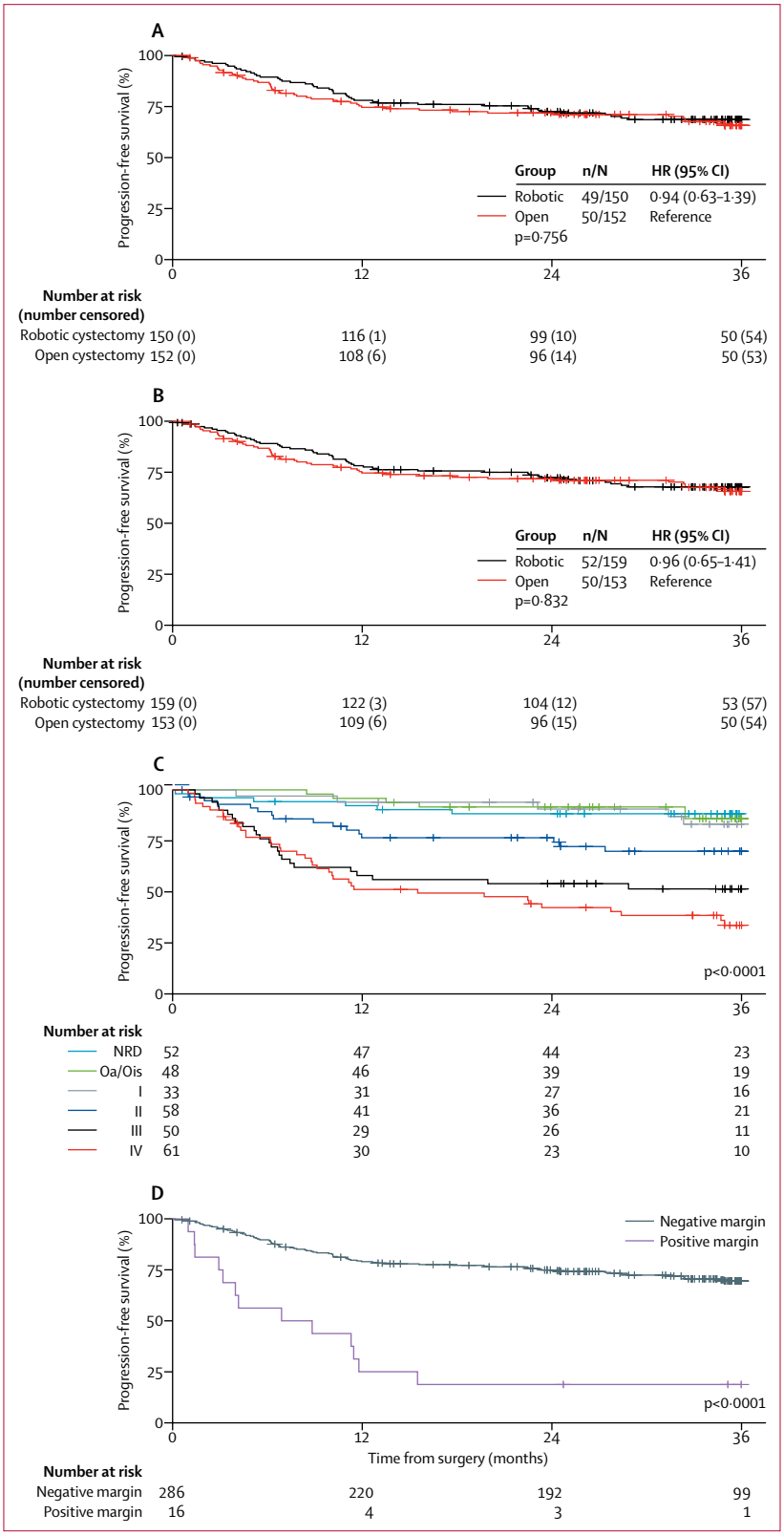
This trial is registered with ClinicalTrials.gov, number NCT01157676.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DJP and IMR had full access to all the data in the study and DJP, IMR, and VV had final responsibility for the decision to submit for publication.

Results

Between July 1, 2011, and Nov 18, 2014, 350 patients were randomly assigned to treatment: 176 to the robotic cystectomy group and 174 to the open cystectomy group (figure 1). Of the 176 patients who were randomly assigned to receive robotic cystectomy, 17 (10%) patients did not have surgery and nine (5%) patients had a different surgery to that they were assigned. Of the 174 patients assigned to receive open cystectomy, 21 (12%) patients did not have surgery and one (1%) patient had robotic cystectomy instead of open cystectomy. Thus, 150 patients in the robotic cystectomy group and 152 patients in the open cystectomy group



were included in the per-protocol analysis set and 159 patients in the robotic cystectomy group and 153 patients in the open cystectomy group were included in the modified intention-to-treat analysis set. Baseline demographic and tumour characteristics were similar between the two groups (table 1; appendix p 10). The distribution of patients by institution and the contribution of individual surgeons is shown in the appendix (p 11).

2-year progression-free survival was 72·3% (95% CI 64·3 to 78·8) in the robotic cystectomy group and 71·6% (95% CI 63·6 to 78·2) in the open cystectomy group (difference 0·7% [95% CI –9·6 to 10·9; p=0·90; $p_{non\text{-}inferiority}$=0·001); showing non-inferiority of robotic cystectomy to open cystectomy. The results of the sensitivity analysis in the modified intention-to-treat population also confirmed the non-inferiority of robotic cystectomy (table 2; figure 2).

At the data cutoff, 28 (19%) of 150 patients in the robotic cystectomy group and 32 (21%) of 152 patients in the open cystectomy group had died of bladder cancer (appendix p 12). Additionally, ten (7%) of 150 patients in the robotic cystectomy group and 11 (7%) of 152 patients in the open cystectomy group had died of causes unrelated to bladder cancer and 11 (7%) and seven (5%) patients were alive with recurrence. The proportion of patients with local recurrences was similar between the treatment groups (six [4%] of 150 patients in the robotic cystectomy group *vs* four [3%] of 152 patients in the open cystectomy group; p=0·54) and local recurrence in the cystectomy bed was also similar (six [4%] patients in the robotic cystectomy group *vs* two [1%] patients in the open cystectomy group; p=0·17; appendix p 12). 33 (22%) of 150 patients in the robotic cystectomy group and 35 (23%) of 152 patients in the open cystectomy group had distant metastases. The most common sites of metastases were the lungs, liver, bone, and extrapelvic lymph nodes. No port site recurrences were reported. During the 2-year follow-up period, ten (7%) of 150 patients in the robotic cystectomy were censored, of whom one (1%) patient was lost to follow-up, and 14 (9%) of 152 patients in the open cystectomy were censored, of whom six (4%) were lost to follow-up.

Progression-free survival was worse with increasing pathological stage (p<0·0001; figure 2C) and in patients with positive surgical margins (p<0·0001; figure 2D). Exploratory subgroup analysis revealed no significant difference between the treatment groups in progression-free survival across all cancer stages (appendix p 13).

Figure 2: **Progression-free survival**
Kaplan-Meier curves for comparison of progression-free survival by treatment group in the per-protocol population (A), and the modified intention-to-treat population (B) and by pathological stage (C) and margin status (D) in the per-protocol population. Follow-up is truncated at 36 months. Vertical lines indicate censored patients. n=patients with progression. N=group size. HR=hazard ratio. NRD=no residual disease.

Estimated blood loss was significantly lower in the robotic cystectomy group than the open cystectomy group (p<0·0001; table 3). The proportion of patients who required intraoperative blood transfusion and postoperative blood transfusion was significantly lower in the robotic cystectomy group than the open cystectomy group (p=0·0002 and p=0·0089, respectively; table 3). Median length of hospital stay was significantly lower in the robotic cystectomy group than the open cystectomy group (p=0·0216; table 3). 40 (29%) of 150 patients in the robotic cystectomy group and 27 (18·5%) of 152 patients in the open cystectomy group stayed in hospital for less than 5 days after surgery (p=0·0407; table 3). Median operating time was significantly longer in the robotic

	Robotic cystectomy (n=150)	Open cystectomy (n=152)	Difference (95% CI)	p value
Patients with blood loss data	148 (99%)	149 (98%)	..	..
Blood loss, mL	300 (200–500)	700 (500–1000)	..	<0·0001
Perioperative transfusion	35/143 (24%)	65/143 (45%)	−21·0 (−31·8 to −10·2)	0·0002
Units of blood transfused	3 (2–5)	4 (2–5)	..	0·46
Intraoperative transfusion	18/139 (13%)	46/136 (34%)	−20·8 (-30·6 to −11·2)	<0·0001
Postoperative transfusion	33/132 (25%)	54/135 (40%)	−15·0 (-26·1 to −3·9)	0·0089
Hospital stay ≤5 days	40/139 (29%)	27/146 (18%)	10·3 (0·5 to 20·1)	0·0407
Length of stay, days	6 (5–10)	7 (6–10)	..	0·0216
Operating time, min	428 (322–509)	361 (281–450)	..	0·0005
Surgical complications within 90 days*				
0	49 (33%)	47 (31%)	..	0·80
I	24 (16%)	20 (13%)	..	..
II	44 (29%)	51 (34%)	..	..
III	29 (19%)	28 (18%)	..	..
IV	0	2 (1%)	..	..
V	4 (3%)	4 (3%)	..	..
Grades I–V *vs* 0	101 (67%)	105 (69%)	−1·8 (−12·3 to 8·8)	0·75
Grades III–V *vs* 0–II	33 (22%)	34 (22%)	−0·4 (−9·0 to 9·8)	0·94
Histopathology classification				
Urothelial	123 (82%)	116 (76%)	..	0·50
Non-urothelial	5 (3%)	4 (3%)	..	..
Negative	19 (13%)	29 (19%)	..	..
Undetermined	3 (2%)	3 (2%)	..	..
T stage†				
T0	22 (15%)	31 (20%)	..	0·70
Ta, Tis	25 (17%)	25 (16%)	..	..
T1	19 (13%)	15 (10%)	..	..
T2	38 (25%)	33 (22%)	..	..
T3	35 (23%)	32 (21%)	..	..
T4a	10 (7%)	14 (9%)	..	..
T4b	1 (1%)	3 (2%)	..	..
N stage†				
Nx or missing	5 (3%)	7 (5%)	..	0·55
N0	110 (73%)	121 (80%)	..	..
N1	13 (9%)	8 (5%)	..	..
N2	17 (11%)	13 (9%)	..	..
N3	5 (3%)	3 (2%)	..	..
Pathological stage†				
No residual disease	22 (15%)	30 (20%)	..	0·45
0is/0a	24 (16%)	24 (16%)	..	..
I	18 (12%)	15 (10%)	..	..
II	29 (19%)	29 (19%)	..	..
III	21 (14%)	29 (19%)	..	..
IV	36 (24%)	25 (16%)	..	..

(Table 3 continues on next page)

	Robotic cystectomy (n=150)	Open cystectomy (n=152)	Difference (95% CI)	p value
(Continued from previous page)				
Lymph node dissection‡				
Extended	76/149 (51%)§	84/152 (55%)	−4·3 (−15·5 to 7·0)	0·46
Standard	73/149 (49%)	68/152 (45%)	..	..
Lymph nodes removed, mean (SD)	23·3 (12·5)	25·7 (14·5)	..	0·13
Positive surgical margin	9 (6%)	7 (5%)¶	1·4 (−3·7 to 6·5)	0·59
Positive bladder margin	6 (4%)	5 (3%)	0·7 (−3·5 to 4·9)	0·74
Positive urethral margin	3 (2%)	4 (3%)	−0·6 (−4·0 to 2·8)	1·00

Data are n (%) or median (IQR), unless specified otherwise. *Graded according to the Clavien-Dindo classification. †Staging according to American Joint Committee on Cancer staging for bladder cancer 7th edition.[35] ‡Standard lymph node dissection included all potential lymph-node-bearing tissue with the lateral limit of the genitofemoral nerve, the distal limit of Cooper's ligament to include the lymph node of Cloquet, the proximal limit of the crossing of the ureter over the common iliac vessels, the medial limit of the bladder to include the tissue medial to the hypogastric artery, and the posterior limit of the floor of the obturator fossa with circumferential mobilisation of the external iliac artery and vein. For extended lymph node dissection the upper limit of the dissection was extended superiorly to the aortic bifurcation. §One patient did not have lymph node dissection. ¶Two patients had positive bladder and urethral margins.

Table 3: **Perioperative and pathological outcomes in the per-protocol population**

	Baseline		3 months		6 months	
	Robotic cystectomy	Open cystectomy	Robotic cystectomy	Open cystectomy	Robotic cystectomy	Open cystectomy
Physical wellbeing, n	116	115	104	102	99	99
Estimated mean score (95% CI)	22·9 (21·8–24·0)	23·4 (22·3–24·6)	23·2 (22·1–24·3)	22·8 (21·6–24·0)	23·2 (22·0–24·3)	23·9 (22·7–25·0)
Social wellbeing, n	113	115	105	100	99	98
Estimated mean score (95% CI)	23·5 (22·2–24·7)	23·5 (22·2–24·8)	23·1 (21·9–24·3)	22·6 (21·3–23·9)	23·3 (22·1–24·5)	23·3 (22·1–24·6)
Emotional wellbeing, n	111	112	98	95	96	91
Estimated mean score (95% CI)	17·5 (16·4–18·6)	17·7 (16·5–18·8)	19·5* (18·4–20·5)	19·9* (18·8–21·0)	19·4* (18·3–20·5)	20·0* (18·9–21·2)
Functional wellbeing, n	115	115	105	100	98	97
Estimated mean score (95% CI)	18·4 (16·8–20·0)	18·4 (16·7–20·1)	17·9 (16·3–19·5)	19·3 (17·6–21·0)	18·5 (16·9–20·1)	19·7 (18·0–21·4)
FACT-BL-Cys, n	115	114	105	100	98	97
Estimated mean score (95% CI)	37·4 (35·0–39·8)	36·7 (34·2–39·2)	37·9 (35·8–40·0)	38·2 (36·0–40·5)	39·3 (37·1–41·4)	39·4 (37·1–41·6)
Trial outcome index, n	115	114	104	100	98	97
Estimated mean score (95% CI)	78·9 (74·6–83·2)	78·9 (74·3–83·5)	79·3 (75·1–83·4)	80·7 (76·3–85·2)	81·1 (77·0–85·3)	83·2 (78·8–87·6)
FACT-G, n	108	112	97	94	95	91
Estimated mean score (95% CI)	82·4 (78·6–86·1)	83·5 (79·5–87·4)	84·2 (80·4–88·1)	85·8 (81·8–89·9)	85·9 (82·1–89·7)	87·4* (83·5–91·4)
FACT-BL-Cys Total, n	108	111	97	94	95	91
Estimated mean score (95% CI)	120·1 (114·5– 125·8)	120·9 (115·0–126·8)	122·8 (117·2–128·3)	125·2 (119·3–131·1)	126·0* (120·4–131·6)	127·5* (121·7–133·3)

n indicates the number of patients who answered each section of the questionnaire. FACT-VCI consists of eight domains (five subscale scores [physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, and FACT-BL-Cys]) and three derived scores (trial outcome index), FACT-G, and FACT-BL-Cys Total. The ranges of scores for each domain are as follows: 0–28 for physical, social, and functional wellbeing; 0–24 for emotional wellbeing; 0–60 for FACT-BL-Cys; 0–116 for FACT-VCI Trial Outcome Index (sum of physical wellbeing, functional wellbeing, and FACT-BL-Cys scores); 0–108 for FACT-G (sum of physical, social, emotional, and functional wellbeing scores); and 0–168 for FACT-BL-Cys Total (sum of physical, social, emotional, and functional wellbeing scores, and FACT-BL-Cys). FACT-VCI=Functional Assessment of Therapy-Vanderbilt Cystectomy Index. FACT BL-Cys=Functional Assessment of Therapy for patients with Bladder Cancer following cystectomy. FACT-G=Functional Assessment of Therapy-General form. *p≤0·05 compared with baseline, using Bonferroni's adjustment for multiple comparisons.

Table 4: **Quality of life outcomes**

cystectomy group than the open cystectomy group (p=0·0005; table 3).

No significant differences in overall complications (grades I–V) were identified between the treatment groups and the proportion of patients who had major complications (grades III–IV) was also similar between the groups (table 3).

Data entry errors identified at the data cutoff that involved soft tissue margin pathology were corrected in ten (7%) of 150 patients in the robotic cystectomy group and two (1%) of 152 patients in the open cystectomy. No significant differences were identified between the treatment groups in tumour histology and staging, extended lymph node dissection (p=0·46), the mean number of lymph nodes removed (p=0·13), and proportion of patients with positive surgical margins (p=0·59; table 3). Of the patients with positive surgical margins, seven (78%) of nine in the robotic cystectomy group and five (71%) of seven in the open cystectomy group had stage T3 bladder cancer or higher.

No significant differences were identified between the treatment groups at any timepoint for all FACT-VCI

endpoints (table 4). In the robotic cystectomy group, the mean estimated score for emotional wellbeing was significantly higher at 3 months (p=0·0007) and 6 months (p=0·0014) than at baseline. Similarly, in the open cystectomy group, the mean estimated emotional wellbeing score was significantly higher at 3 months (p=0·0007) and at 6 months (p=0·0007) than at baseline (table 4, appendix p 14). Both groups had significant improvement in mean total FACT-VCI score 6 months after surgery compared with baseline (table 4). Cost data was specified as a secondary endpoint in the protocol, but data could not be collected from all sites due to proprietary reasons. Additionally, considerable heterogeneity was identified between the institutions that shared cost data, and thus the available data was unsuitable for analysis.

Common adverse events in both groups are shown in table 5. 101 (67%) of 150 patients in the robotic cystectomy group and 105 (69%) of 152 patients in the open cystectomy group had adverse events. The most common adverse events were urinary tract infection (53 [35%] in the robotic cystectomy group *vs* 39 [26%] in the open cystectomy group) and postoperative ileus (33 [22%] in the robotic cystectomy group *vs* 31 [20%] in the open cystectomy group).

Discussion

The IDEAL initiative has recommended incremental steps towards the robust assessment of surgical innovation.[2] Several investigators involved in this study were early adopters of robotic technology in bladder cancer. Similar to most surgical studies, the development of robotic cystectomy did not follow the IDEAL recommendations in stage 2a (development) studies, however, stage 2b was successfully completed through two single-centre feasibility trials.[8,16] Results from the feasibility studies guided the investigators towards obtaining funding for design and successful accrual in this phase 3 multicentre study. Few randomised trials have assessed surgical technology and previous studies[17,18] comparing open surgery with robotic surgery have focused on perioperative and functional endpoints.

Robotic surgery has been proposed to improve perioperative recovery; however, it is associated with high costs and an extensive learning curve. To the best of our knowledge, no prospective multicentre studies have compared the oncological outcomes of robotic surgery with that of open surgery. Thus, we designed this study to investigate whether robotic cystectomy was non-inferior to open cystectomy. The results of this study could potentially be used to plan further superiority trials. The nature of the surgical procedures necessitated an open-label design; however, we do not believe this affected the assessment of primary and secondary outcomes in this study.

In this non-inferiority study, 2-year progression-free survival in the robotic cystectomy group (72%) was

	Open cystectomy (n=152)	Robotic cystectomy (n=150)
Gastrointestinal		
Anastomotic bowel leak	0	3 (2%)
Colitis	6 (4%)	6 (4%)
Colonic perforation	1 (1%)	0
Ileal perforation	2 (1%)	0
Ileus	31 (20%)	33 (22%)
Small intestinal obstruction	5 (3%)	4 (3%)
Infections		
Urinary tract infection	39 (26%)	53 (35%)
Sepsis	16 (11%)	15 (10%)
Superficial wound infection	18 (12%)	11 (7%)
Deep wound infection	10 (7%)	3 (2%)
Intra-abdominal infection	3 (2%)	7 (5%)
Stoma site infection	3 (2%)	2 (1%)
Renal and urinary		
Acute renal failure	19 (13%)	17 (11%)
Renal insufficiency requiring dialysis	1 (1%)	0
Urinary fistula	2 (1%)	3 (2%)
Ureteral stricture	10 (7%)	13 (9%)
Injury and procedural complications		
Intestinal stoma leak	0	1 (1%)
Intraoperative gastrointestinal injury	1 (1%)	1 (1%)
Seroma	0	3 (2%)
Ureteric anastomotic leak	5 (3%)	3 (2%)
Wound dehiscence	3 (2%)	0
Wound disruption	11 (7%)	7 (5%)
Respiratory		
Pneumonia	6 (4%)	7 (5%)
Aspiration	0	2 (1%)
Failure to wean from vent within 48 h of surgery	1 (1%)	1 (1%)
Respiratory failure	1 (1%)	2 (1%)
Re-intubation	4 (3%)	5 (3%)
Pulmonary oedema	..	1 (1%)
Pleural effusion	1 (1%)	1 (1%)
Vascular disorders		
Lymphocele	3 (2%)	4 (3%)
Pulmonary embolism	4 (3%)	4 (3%)
Thromboembolic event	12 (8%)	7 (5%)
Cardiac disorders		
Acute coronary syndrome	4 (3%)	1 (1%)
Atrial fibrillation	6 (4%)	7 (5%)
Atrial flutter	..	1 (1%)
Cardiac event with cardiopulmonary resuscitation	1 (1%)	1 (1%)
Myocardial infarction	1 (1%)	3 (2%)
Sick sinus syndrome	1 (1%)	0
Ventricular tachycardia	2 (1%)	1 (1%)

Data are n (%).

Table 5: **Common grade 1–5 adverse events in the per-protocol population**

non-inferior to that of the open cystectomy group (72%; difference 0·7%, 95% CI –9·6 to 10·9). Robotic surgery was associated with decreased blood loss, reduced blood transfusion rates, and a shorter length of hospital stay, but a longer duration of surgery, than open surgery. No differences were identified in complication rates, lymph node yields, positive margins, or QoL outcomes between the two treatment groups.

The 2-year progression-free survival results in this trial are similar to previous single and large multicentre retrospective studies.[19,20] The 2-year interval was selected because most bladder cancer recurrences manifest within this time, and patient outcomes at 2 years correlate well with outcomes at longer durations.[19,21] The treatment groups were well balanced with regard to pathological features and the proportion of patients with non-organ confined cancer (38% in the robotic group and 36% in the open group), which was similar to previous studies. These data suggest that the results might be generalisable.[19,20]

Single-centre randomised, and larger retrospective studies have reported no significant increase in risk of positive surgical soft-tissue margins for robotic cystectomy.[8,16,18,20] This could be because of the smaller sample sizes used in previous randomised studies, and selection biases in retrospective studies (eg, a robotic approach might be preferred for less advanced or biologically favourable cancers). The results of this trial indicate that a similar number of patients who have robotic surgery can achieve negative surgical margins compared with patients who have open radical cystectomy and mitigates concerns regarding absence of tactile feedback and excessive manipulation of the cystectomy specimen.[20,22]

Robotic cystectomy has been reported to increase risk of peritoneal carcinomatosis, port site recurrences, and extra pelvic lymph node metastases, which might be caused by tumour seeding associated with pneumoperitoneum, excessive manipulation of the cystectomy specimen, and breach of the specimen bag.[6] In this trial, we found no difference in patterns of local and distant recurrences between the two groups, reinforcing the safety of the robotic approach.

Surrogates of surgical quality that have a direct effect on oncological outcomes in bladder cancer have been defined. These include major complications, extent of lymph node dissection, lymph node count, and positive margins.[23,24] We found no significant difference in the overall and major complication rates between the two treatment groups in our study, which is concordant with results of single-centre randomised studies and other reports, and refutes retrospective study comparisons[4,8–10,16,18] reporting significantly lower complication rates for robotic surgery than open surgery, which is likely to be a result of selection bias. The perioperative parameters of blood loss, transfusion rates, length of stay, and surgery duration in this study across both groups compare favourably to the results of previous studies.[4,10] The equal distribution of non-organ confined cancers and the 3% conversion rate to open surgery in the robotic group reflect the proficiency of participating surgeons in the robotic approach. The extent of lymph node dissection, lymph node counts, and positive margin rates were similar between the two groups and are similar to contemporary studies.[13,20]

Radical cystectomy with urinary diversion is known to substantially affect patient QoL. This study showed no difference between the open cystectomy and robotic cystectomy groups with regard to QoL. An early robotic study[25] reported that QoL returns to, or exceeds, that at baseline by 3–6 months after cystectomy. In a previous pilot trial[26] no significant difference in QoL was found between robotic and open cystectomy. Two subsequent single-centre trials[18,27] have reported similar results.

Buxton's law states that it is always too early for rigorous assessment of a new surgical technique, until, unfortunately, it is suddenly too late.[28] Generally, the clinical community is reluctant to subject new surgical innovation to scientific rigor early on because procedures often have an extensive learning curve, and by the time the technique is widely adopted, it is often too late to do rigorous trials because it would be unethical to deny patients access to cutting-edge care. Thus, thorough evaluation of new surgical innovations is often avoided before best practice is determined. The focus on oncological endpoints rather than the traditionally studied endpoints of perioperative morbidity and cosmesis in this study might have contributed to the success of our trial.

Participating centres were academic medical centres and surgeons were either fellowship-trained or had a dedicated uro-oncology practice. All centres did not contribute equally to the study and the patients recruited represent only a percentage of all patients with bladder cancer treated at that institution during the study period.

Another limitation is that multiple surgeons were involved. However, all participating surgeons were required to have done at least ten open or robotic cystectomies in the year before the study; therefore, only surgeons with substantial experience were selected. Many surgeons did both procedures during the trial; however, at some centres robotic and open cystectomies were done by different surgeons on the basis of individual expertise. The effect of this internal distribution of surgical approach on outcomes is likely to be minimal considering the superior quality of cystectomy in both groups.

Although centralised pathological review was not done, all participating sites adhered to standardised reporting guidelines and audited pathology data before final data analyses.

Specific components of treatment, such as chemotherapy use and extended lymph node dissection were

left to individual surgeons' discretion, which introduces a potential source of bias. However, these treatments were equally balanced between groups and we believe this would have had a minimal effect on the outcome.

All urinary diversions in this study were extracorporeal. Intracorporeal urinary diversion has been reported to improve perioperative recovery compared with extracorporeal diversion.[29] However, this procedure has an extensive learning curve with no conclusive evidence of significant improvement in perioperative outcomes.[29] Therefore, a prospective comparison between extracorporeal and intracorporeal diversion in patients with bladder cancer would be of value.

Reliable cost data was unavailable because several institutions were unwilling to provide data on contracted rates. Legal limitations prohibit health systems from sharing cost or contracted charge information according to US insurance laws. Moreover, insurance companies pay hospitals a percentage of the total cost for procedures, which are substantially inflated compared with the actual cost. Whether the high costs of robotic surgery due to equipment, disposables, and increased operating time will be offset by improvements in aspects of perioperative recovery with this approach remains unclear. Increased surgical experience combined with more competition within industry might decrease the cost of robotic technology over time.

Our study shows that phase 3 multicentre randomised trials assessing technology-based surgical innovations can be done successfully. In this study, the use of robot-assisted radical cystectomy for bladder cancer resulted in a 2-year progression-free survival that was non-inferior to that of open surgery.

Increased adoption of robotic technology in surgery should lead to future randomised trials across different organ sites to assess the true clinical value provided by novel technology.

Contributors

DJP and IMT conceived and designed the study. All authors were involved in data collection, data analysis, and data interpretation, and all authors drafted and reviewed the manuscript.

Declaration of interests

EPC reports personal fees from Intuitive Surgical outside the submitted work. MEW reports grants from the National Institutes of Health (NIH) during the study, and outside the submitted work. AZW reports grants from the University of Michigan during the study. BRK reports grants from the National Cancer Institute during the study; and grants from Photocure, Roche-Genentech, Genomic Health, Myriad Genetics, Spectrum, and FKD Therapies, outside the submitted work. MT reports grants from the NIH during the study. TLK reports grants from the NIH during the study. DAB reports grants from the NIH, during the study; and personal fees from AstraZeneca, Tolmar Pharmaceuticals, and Janssen, outside the submitted work. ASK reports advisory board fees from Profound, Sanofi-Aventis, and Janssen, outside the submitted work. CJW reports grants from Myriad Genetics and personal fees from Abbott Molecular, outside the submitted work. MSC has served on advisory boards for Astellas Pharma US, MDxHealth, Janssen, Bayer Healthcare, CicloMed, Abbott Laboratories, Tolmar Pharmaceuticals, Genomic Health, Altor Bioscience, Photocure, and Takeda Pharmaceutical; and reports consultancy fees from Myovant Sciences, TesoRx Pharma, and Pacific Edge Diagnostics. All other authors declare no competing interests.

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