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Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes

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Abstract

Background: Open radical cystectomy (ORC) has proven to be an important component in the treatment of high-risk bladder cancer (BCa). ORC surgical morbidity remains high; therefore, minimally invasive surgical techniques have been introduced in an attempt to improve patient outcomes.
Objective: To compare cancer outcomes in BCa patients managed with ORC or robotic-assisted radical cystectomy (RARC).
Design, setting, and participants: A prospective, randomized trial was completed between 2010 and 2013. Patients were randomized to ORC/pelvic lymphadenectomy (PLND) or RARC/PLND, with all undergoing open/extracorporeal urinary diversion. Median follow-up was 4.9 (IQR: 3.9–5.9) yr after surgery among surviving patients.
Outcome measurements and statistical analysis: Secondary outcomes to the trial included recurrence-free, cancer-specific, and overall survival.
Results and limitations: The trial randomized 118 patients who underwent RC/PLND and urinary diversion. Sixty were randomized to RARC and 58 to ORC. Four RARC-assigned patients refused randomization and received ORC; however, an intention to treat analysis was performed. No differences were observed in recurrence (hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 0.69–2.36; $p = 0.4$) or cancer-specific survival ($p = 0.4$). No difference in overall survival was observed ($p = 0.8$). However, the pattern of first recurrence demonstrated a nonstatistically significant increase in metastatic sites for those undergoing ORC (sub-HR [sHR]: 2.21; 95% CI: 0.96–5.12; $p = 0.064$) and a greater number of local/abdominal sites in the RARC-treated patients (sHR: 0.34; 95% CI: 0.12–0.93; $p = 0.035$). The major limitation to this study is that the trial was not powered to determine differences in cancer recurrences, survival outcomes, or patterns of recurrence.
Conclusions: The secondary outcomes from our randomized trial did not definitively demonstrate differences in cancer outcomes in patients treated with ORC or RARC. However, differences in observed patterns of first recurrence highlight the need for future studies.
Patient summary: Of 118 patients randomly assigned to undergo radical cystectomy/pelvic lymphadenectomy and urinary diversion, half were assigned to open surgery and half to robot-assisted techniques. We found no difference in risk of recurring or dying of bladder cancer between the two groups.

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1. Introduction

Radical cystectomy (RC) with regional pelvic lymphadenectomy (PLND) is the established standard of care for treating high-risk bladder cancer (BCa) [1,2]. BCa is common in older individuals and strongly linked to smoking exposure. Performing extensive pelvic surgery and reconstruction of the urinary system in an elderly, comorbid population carries significant surgical risks. The development of minimally invasive surgical techniques has been widely used in a variety of surgical procedures. One major goal associated with the adaptation of minimally invasive techniques is to minimize surgical morbidity and improve recovery.

Robot-assisted RC (RARC) was introduced in hopes of decreasing the substantial morbidity following standard of RC and urinary diversion. Several retrospective series had reported perioperative outcomes including complications following RARC with either open or intracorporeal techniques [3–6]. We reported our results of a randomized controlled study designed to compare complications between open RC (ORC) and RARC [7,8]. In that trial, we reported no large differences in 90-d overall complications, high-grade complications, or hospital length of stay. Pathologic outcomes including positive soft tissue margin (PSTM) rates and lymph node yield were similar between open and robotic techniques. Margin rates and lymph node yields were similar to previously reported benchmarks.

Long-term oncologic outcomes following RARC have not been well documented in the reported literature. Here, we describe the oncologic outcomes from our ORC versus RARC randomized controlled trial, including the secondary endpoints of recurrence-free survival, overall survival, and patterns of first recurrence.

2. Patients and methods

2.1. Patients

Patients with BCa scheduled to undergo RC and PLND were recruited from the urology clinics at Memorial Sloan Kettering Cancer Center (MSKCC) between March 2010 and March 2013. The study protocol was approved by the Institutional Review Board, and all patients were required to provide written consent prior to enrollment and surgery. Patients were randomized 1:1 to undergo RARC or ORC using MSKCC's Clinical Research Database, a secure system that ensures allocation concealment.

Eligible patients were medically fit for RC, aged $\geq$18 yr, and had clinical stage Ta-T3/N0-3/M0 BCa. Patients with a prior history of pelvic radiation, clinical stage T4, prior extensive open abdominal surgery, or any clinical contraindication to minimally invasive surgery were excluded. Postoperatively all patients were followed every 3–6 mo with routine history and physical exams, diagnostic imaging of the chest/abdomen/pelvis, urine cytology, and complete blood work. Additional diagnostic imaging or investigations were conducted at the discretion of the surgical team.

2.2. Surgical intervention

Complete details regarding the surgical intervention have been previously described [7]. Men underwent removal of the prostate, and women underwent hysterectomy and bilateral salpingo-oophorectomy if these organs were present. The extent of PLND was left to the discretion of the surgeon based on clinician preference and judgment, and was determined prior to randomization. At a minimum, the primary drainage regions (hypogastric, obturator, external iliac) were removed bilaterally. Extended dissections removed at least the lymph nodes overlying the aortic bifurcation and continued to the take-off of the inferior mesenteric artery.

2.3. Statistical analysis

Details of the trial design and randomization have been previously described [7]. The date of the first documented BCa recurrence was identified from clinical records, radiological findings, or pathological specimens. Cancer-specific mortality and all-cause mortality were recorded from institutional and clinical records.

Kaplan–Meier methods were used to estimate recurrence and survival probabilities after RC on an intention to treat basis, and the log-rank test was used to compare differences in recurrence and cancer death rates between the RARC and ORC groups. Greenwood's variance estimates were used to calculate confidence intervals (CIs) for differences in recurrence and cause-specific death rates after RC. Recurrent BCa was characterized by the site of disease detection in one of the three categories: (1) local pelvic recurrence (soft tissue recurrences within or surrounding the cystectomy bed, pelvis, rectum, or pelvic nodal regions), (2) abdominal recurrence (abdominal wall, peritoneal carcinomatosis, or other intraperitoneal implants within the abdominal cavity), and (3) distant recurrence (lung, liver, bone, extrapelvic lymph nodes). New urothelial-based tumors (urethra, ureters) were evaluated separately. Based on observed recurrences, we undertook an analysis that was not prespecified in the study protocol to test for a pattern in the site of the first recurrence by treatment arm. Using competing risks methods, we compared local pelvic recurrence, abdominal recurrence, and distant recurrence in three separate analyses. We also grouped local pelvic recurrence and abdominal recurrence into a single local/regional recurrence group and repeated the competing risk analysis. For each of these analyses, the competing events were death from another cause or recurrence to another site. All analyses were conducted in Stata 15.0 (College Station, TX, USA), and the analytic code is available at https://github.com/ddsjoberg/manuscript-code-share.

3. Results

3.1. Patient population

Patient demographics and disease characteristics of the two groups were similar (Table 1). Pathologic staging of the two groups was not significantly different (Table 1). Pathologic stage T4 was found in five patients (8.3%) undergoing RARC and four (6.9%) undergoing ORC. There was no difference in the lymph node yield based on the extent of dissection and PSTM rate between RARC (3.6%) and ORC (4.8%).

Among the 118 enrolled patients, the median follow-up was 4.9 (IQR: 3.9–5.9) yr after surgery among surviving patients. Overall, there were 45 patients who experienced recurrences (Table 2). A total of 36 deaths were observed, 19 of which were from BCa. One patient who underwent ORC died from surgical complication 3 mo after RC.

We found that recurrence-free survival and BCa-specific survival were similar between the robot and open surgery arms ($p = 0.4$ and $p = 0.4$, respectively; Figs. 1 and 2). Results were similar for risk estimates of all-cause mortality after surgery in the RARC and ORC arms ($p = 0.8$; Fig. 3). Risk of

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