Perioperative and 5-Year Oncological Outcomes Following Open Radical Cystectomy for 200 Patients: A Single Center Experience

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ABSTRACT

INTRODUCTION: Contemporary benchmarks of the short-term and long-term outcomes of open radical cystectomy (ORC) that can be used for future comparison of minimally invasive techniques are incomplete. The purpose of this prospective study was to evaluate the perioperative and 5-year oncological results of ORC with urinary diversion.

METHODS: Between 2004 and 2009, 200 patients undergoing ORC with urinary diversion were prospectively enrolled. Indications for ORC included: (1) muscle-invasive bladder cancer detected by transurethral resection, or (2) high-grade stage Ta, T1, or carcinoma in situ that was refractory to repeated transurethral resection and intravesical immunotherapy or chemotherapy. Patients with metastatic disease were excluded. Mean patient age was 65.1 years. Perioperative, histopathologic, and postoperative follow-up data were recorded and analyzed statistically.

RESULTS: Ileal conduits were constructed in 159 (79.5%) patients; an ileal orthotopic neobladder (Studer’s procedure) was constructed in 41 (20.5%) patients. Mean operating time was 275 minutes. Mean estimated blood loss was 690 mL. Blood transfusion was required in 37 (18.5%) patients. Mean hospital stay was 6.1 days. Major and minor complications were recorded in 16 (8%) and 31 (15.5%) of the patients, respectively. Perioperative mortality was recorded in 2 (1.5%) patients. Pathologically organ-confined and nonorgan-confined cancer was found in 135 (67.5%) and 65 (32.5%) patients, respectively; 33 (16.5%) patients had pathologically confirmed lymph nodes. Median follow-up was 60.1 months. Local recurrence and distant metastases were recorded in 16 (8%) and 9 (4.5%) patients, respectively. The 5-year disease-free survival, cancer-specific survival, and overall survival rates were 75.5%, 71.5%, and 63.5%, respectively. Survival rates were significantly higher for patients with organ-confined cancers and negative lymph nodes.

CONCLUSIONS: Open radical cystectomy has an acceptable perioperative morbidity and mortality, along with a favorable 5-year oncological efficacy. Minimally invasive techniques need long-term prospective comparison with this approach before they can be accepted as a standard treatment for urinary bladder malignancy.

KEYWORDS: Urinary bladder; Carcinoma; Radical cystectomy

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Abbreviations and Acronyms
CT = computed tomography
LRC = laparoscopic radical cystectomy
ORC = open radical cystectomy
RRC = robotic radical cystectomy
TCC = transitional cell carcinoma
INTRODUCTION

Bladder malignancy is the 4th most common cancer in males, after prostate, lung, and colorectal cancers. Its incidence is nearly 3 times more common in males than females [1]. The standard treatment for muscle-invasive bladder cancers and high-grade nonmuscle invasive bladder cancers that are refractory to intravesical immunotherapy has been the open radical cystectomy (ORC) in males and anterior exenteration in females, coupled with en bloc pelvic lymphadenectomy [1-3]. Traditionally, radical cystectomy has been associated with significant morbidity and mortality. However, due to improvements in surgical and anesthesia techniques as well as perioperative intensive care and monitoring, the mortality and morbidity of ORC have been reduced to 1%-3% and 25%-35%, respectively, in recently published series [1-6].

Laparoscopic surgery for kidney and prostate cancers has produced excellent perioperative and long-term oncological outcomes, thus encouraging its application in bladder cancers. Although a few research groups have demonstrated short-term and intermediate-term oncological efficacy of laparoscopic radical cystectomy (LRC) that is comparable to the open approach, the long-term oncological outcomes are still under scrutiny [7-10]. Surgical expertise requirements, longer operative time, and potentially limited pelvic lymphadenectomy also restrict its application. Recently, robotic radical cystectomy (RRC) was introduced. This procedure provides all of the advantages of minimally invasive surgery with a shorter surgeon learning curve, when compared with standard laparoscopy. However, the cost, availability, and lack of long-term oncological outcomes has limited the application of this approach [11-14].

Surgeons must be fully informed about the differences in morbidity and mortality between minimally invasive and open-surgery techniques in order to make informed choices. Contemporary benchmarks of the short-term and long-term outcomes of open surgery that can be used for future comparison of minimally invasive techniques are incomplete. Although some reports from large-volume centers are available, it is important to know if these results are similar when surgeries are performed at smaller institutions. Therefore, the purpose of the present prospective investigation was to evaluate the perioperative and 5-year oncological results of 200 cases of ORC with urinary diversion.

METHODS

The prospective investigation was conducted between 2004 and 2009. The study was approved by the ethical committee of Safdarjang Hospital, New Delhi, India. All patients provided informed consent.

Participants

All patients undergoing ORC and urinary diversion for urinary bladder malignancy were considered for this study. The indications for ORC included: (1) muscle-invasive bladder cancer detected by transurethral resection, or (2) high-grade stage Ta, T1, or carcinoma in situ that was refractory to repeated transurethral resection and intravesical immunotherapy or chemotherapy. Patients with metastatic disease were excluded. Patients with severe cardiopulmonary illnesses or chronic diseases that made them unfit for the radical procedure were also excluded from the study.

All patients underwent a preoperative metastatic workup including blood tests, chest X-ray, contrast-enhanced computed tomography (CT) of the abdomen and pelvis, and bone scan (when indicated).

A total of 200 patients were enrolled in the study. Table 1 contains the demographic profile of the patients. The mean age of the participants was 65.1 years (SD, 9.2; range, 32-74); 135 patients were male and 65 were female. The mean American Society of Anesthesiologists (ASA) score was 2.6. The mean body mass index (BMI) was 26.8. Thirty-seven patients (18.5%) had a previous abdominal surgery, and 25 patients (12.5%) had a previous abdominal radiation. The clinical stage was nonmuscle invasive in 14.5% and muscle invasive in 85.5%. Nineteen patients (9.5%) received neoadjuvant chemotherapy, 27 patients (13.5%) received radiotherapy, and 23 patients (11.5%) received intravesical therapy.

Table 1. The Demographic Profile of All Patients (N = 200).

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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Measure</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>65.1 (32-74)</td>
</tr>
<tr>
<td>Sex, n</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>135</td>
</tr>
<tr>
<td>Female</td>
<td>65</td>
</tr>
<tr>
<td>ASA score, mean</td>
<td>2.6</td>
</tr>
<tr>
<td>BMI score, mean, Kg/m2</td>
<td>26.8</td>
</tr>
<tr>
<td>Previous abdominal surgery, n (%N)</td>
<td>37 (18.5)</td>
</tr>
<tr>
<td>Previous abdominal radiation, n (%N)</td>
<td>25 (12.5)</td>
</tr>
<tr>
<td>Clinical stage, n (%N)</td>
<td></td>
</tr>
<tr>
<td>Nonmuscle invasive, &lt;T2</td>
<td>29 (14.5)</td>
</tr>
<tr>
<td>Muscle invasive, T2-T4</td>
<td>171 (85.5)</td>
</tr>
<tr>
<td>Neoadjuvant therapy, n (%N)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy, MVAC</td>
<td>19 (9.5)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>27 (13.5)</td>
</tr>
<tr>
<td>Intravesical therapy, n (%N)</td>
<td></td>
</tr>
<tr>
<td>BCG</td>
<td>23 (11.5)</td>
</tr>
<tr>
<td>Chemotherapy, mitomycin</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, American Society of Anesthesiologists; BCG, bacillus Calmette-Guerin; BMI, body mass index; MVAC, methotrexate, vinblastine, adriamycin, cisplatin.
Anesthesiologists (ASA) score and body mass index (BMI) scores were 2.6 and 26.8, respectively. Previous abdominal surgery and radiation were performed for 18.5% and 12.5% of the patients, respectively. The cancer was clinically nonmuscle invasive (<T2) in 14.5% of the patients and clinically muscle invasive (T2-T4) in 85.5% of the patients. Previous treatment of locally advanced disease included neoadjuvant chemotherapy (gemcitabine and cisplatin) for 9.5% of the patients and neoadjuvant radiotherapy for 13.5% of the patients. The majority of these patients received neoadjuvant therapy at another institution prior to referral to our institution. A history of intravesical bacillus Calmette-Guerin (BCG) and mitomycin therapy was recorded in 11.5% and 3% of the patients, respectively.

Procedures

The indications and contraindications for orthotopic ileal neobladder (using Studer’s technique) and ileal conduit reconstruction in this study conformed to criteria set by guidelines of European Association of Urology on bladder cancer [15]. The surgery was performed with en bloc excision of the bladder, prostate, and seminal vesicles in males and en block excision of the uterus, ovaries, and anterior vagina in females. Bilateral standard pelvic lymph node dissection was performed in all cases with the following limits: (1) cranially, bifurcation of common iliac artery; (2) caudally, lymph node of cloquet; (3) laterally, genitofemoral nerve (including obturator lymph nodes).

The lymph node packets were sent separately for histopathological examination. The surgical margins were considered positive on demonstration of the tumor at inked margins of the specimen.

Each patient’s demographic profile, perioperative outcomes, histopathological results, and follow-up outcomes were entered into a computerized database. Any death occurring within 30 days of the operation or before discharge was considered as a perioperative mortality.

Patients received follow-up evaluations postoperatively every 3 months for the first 2 years, every 6 months for the next 3 years, and then annually. During each visit, detailed history, physical examination, routine blood tests, chest X-ray, and urine cytology were performed. An abdominopelvic contrast-enhanced CT was performed biannually. Upper tract monitoring was done yearly with either intravenous urography or loopogram, depending on the patient’s serum creatinine level.

Data Analysis

The outcome measures were: (1) perioperative data including the length of surgery and hospital stay, amount of blood loss, and need for transfusion; (2) major and minor complications; (3) histopathological results; (4) follow-up results, including local recurrence and distant metastases. The Kaplan-Meier analysis with log rank comparison was performed to estimate 5-year disease-free survival, 5-year cancer-specific survival, and 5-year overall survival.

RESULTS

Perioperative Outcomes

Table 2 contains a summary of the perioperative outcomes. Ileal conduits were constructed in 159 (79.5%) patients; an ileal orthotopic neobladder (Studer’s procedure) was constructed in 41 (20.5%) patients. Overall mean operating time was 275 minutes (mean ileal conduit time, 262 minutes; mean ileal orthotopic neobladder time, 288 minutes). The mean estimated blood loss was 690 mL, with 37 (18.5%) patients requiring perioperative blood transfusions. The mean hospital stay was 6.1 days.

Complications

Table 3 contains a summary of the major and minor complications encountered in this study. Major complications were seen in 16 (8%) patients. Four patients had significant intraoperative bleeding due to inadvertent damage to accessory pudendal vessels. One patient had a rectal serosal tear due to locally advanced malignancy that abutted the rectum; this patient had a history of pelvic radiotherapy. The tear was diagnosed intraoperatively and managed with interrupted stitches and a rectal tube. Two patients had a bowel anastomosis leak that was diagnosed on the 4th and 5th postoperative day, respectively. They underwent exploratory laparotomy with ileostomy formation, which was subsequently closed after 3 weeks.

Table 2. Perioperative Outcome Measures for All Patients (N = 200).

months. Two patients were diagnosed with subacute intestinal obstruction on the 5th and 6th postoperative day, respectively; the obstruction was managed conservatively. Two (1%) patients died in the perioperative period: 1 due to myocardial infarction and 1 due to severe chest infection (this patient had a prior history of cardiopulmonary disease).

Minor complications were present in 31 (15.5%) patients. Paralytic ileus was the most common minor complication, seen in 15 (7.5%) patients and managed conservatively. One patient had urine leak from ureteroileal anastomosis that was diagnosed on the 4th postoperative day and managed conservatively.

Histopathology

Histopathological results are summarized in Table 4. Transitional cell carcinoma (TCC) was found in 190 (95%) patients. Pathologically organ-confined malignancy (≤ pT2) was found in 135 (67.5%) patients. Nonorgan-confined malignancy (> pT2) was found in 65 (32.5%) patients. The mean number of lymph nodes identified on specimen was 17 (range, 7-26). A total of 33 (16.5%) patients had histologically confirmed positive lymph nodes. All patients with positive lymph nodes received adjuvant chemotherapy (gemcitabine and cisplatin) after surgery. High and low grades (according to WHO-ISUP classification) were found in 29% and 71% of the patients, respectively. Three (1.5%) patients had positive distal surgical margins. All of these patients had locally advanced malignancy and later underwent urethrectomy.

Follow-up Evaluations and Survival Outcomes

Follow-up results are summarized in Table 5. The overall median follow-up period was 53.1 months, which was comparable for patients with both organ-confined and nonorgan-confined disease (P = .32). Local recurrence was recorded in 16 (8%) patients. Distant metastases were recorded in 9 (4.5%) patients, occurring in the liver (n = 5), lungs (n = 2), bones (n = 1), and brain (n = 1).

The 5-year overall survival, disease-free survival, and cancer-specific survival were 63.5%, 75.5%, and 71.5%, respectively. The results were further analyzed for patients with organ confined
Nayan K Mohanty, Anup Kumar, Pawan Vasudeva, Manoj Jain, Sanjay Prakash, Rajender P Arora

Most deaths occurring within the first 3 years after radical cystectomy were attributed to bladder cancer. However, after 3 years of follow-up, most deaths were due to other unrelated comorbid diseases (e.g., myocardial infarction, cerebrovascular stroke).

**DISCUSSION**

Urinary bladder malignancy is the second most common genitourinary malignancy, with TCC comprising nearly 90% of all primary bladder tumors. Although the majority of patients present with superficial bladder tumors, 20% to 40% either

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### Table 5. Follow-up Results Showing Recurrence, Metastases, and Survival Rates According to Histopathological Stages.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Total (N = 200)</th>
<th>≤pT2a (n = 135)</th>
<th>&gt;pT2b (n = 65)</th>
<th>P</th>
<th>pN0 (n = 167)</th>
<th>pN1-pN2 (n = 33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up length, months</td>
<td>60.1</td>
<td>61.2</td>
<td>62.1</td>
<td>.32</td>
<td>63.5</td>
<td>62.7</td>
<td>.44</td>
</tr>
<tr>
<td>Range</td>
<td>14-72</td>
<td>13-69</td>
<td>11-70</td>
<td></td>
<td>16-71</td>
<td>14-69</td>
<td></td>
</tr>
<tr>
<td>Local recurrence, n (%N)</td>
<td>16 (8)</td>
<td>4 (2)</td>
<td>12 (6)</td>
<td></td>
<td>3 (1.5)</td>
<td>13 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Distant metastases, n (%N)</td>
<td>9 (4.5)</td>
<td>3 (1.5)</td>
<td>6 (3)</td>
<td></td>
<td>2 (1)</td>
<td>7 (3.5)</td>
<td></td>
</tr>
<tr>
<td>5-year survival rates, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease-free</td>
<td>75.5</td>
<td>73.3</td>
<td>56.9</td>
<td>.02</td>
<td>78.4</td>
<td>27.2</td>
<td>.01</td>
</tr>
<tr>
<td>Cancer-specific</td>
<td>71.5</td>
<td>71.1</td>
<td>52.3</td>
<td>.01</td>
<td>76.0</td>
<td>24.2</td>
<td>.01</td>
</tr>
<tr>
<td>Overall</td>
<td>63.5</td>
<td>67.4</td>
<td>50.7</td>
<td>.01</td>
<td>68.8</td>
<td>21.2</td>
<td>.01</td>
</tr>
</tbody>
</table>

*a*Organ confined; *b*Nonorgan confined

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**Figure 1a. Kaplan-Meier Curve Showing Recurrence-Free Survival for Patients With Organ-Confined (≤ pT2)/Nonorgan-Confined Cancers (> pT2).**

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**Figure 1b. Kaplan-Meier Curve Showing Recurrence-Free Survival for Patients With pN0/pN1-pN2 Cancers.**

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present with or develop muscle-invasive disease [1-3]. Muscle-invasive TCC of the bladder is generally a lethal disease that requires aggressive therapy; if untreated, fewer than 15% of patients survive for 2 years. The optimal goals of treatment for any invasive bladder cancer should include: (1) acceptable morbidity and mortality, (2) long-term oncological efficacy, (3) prevention of pelvic recurrence or development of metastatic bladder cancer, and (4) an excellent quality of life [4-6].

ORC has been the gold standard for treatment of muscle-invasive and high-risk superficial tumors that are resistant to intravesical therapy [1-6,16,17]. However, this is a formidable procedure that has been associated with significant morbidity and mortality. LRC has been used recently by urologists in an attempt to minimize these effects. Very few prospective comparisons demonstrating the oncological efficacy of ORC and LRC are available in the literature [7-10,18]. Extracorporeal urinary diversion has been used in most of the published series. Some of these studies have shown less blood loss and postoperative pain and earlier recovery of bowel function in patients receiving LRC. Operative time for LRC is increased when compared with ORC. However, these observations have not been corroborated by some other investigators. Recently, RCC has been used as a minimally invasive option for bladder cancer. It has advantages of 3-D vision, no hand tremors, and shorter operator learning curve when compared with LRC. Very few published series comparing RRC and ORC are available [11-14]. Wang et al [14] reported that RRC has operative and perioperative benefits compared with the open approach, without compromising pathological measures of early oncological efficacy such as lymph node yield and margin status. However, their study included only 54 patients and they did not report long-term oncological outcome [14].

We have reported a prospective series of 200 patients receiving ORC from a single institution. This is one of the largest prospective series on ORC reported from India. The demographic profile of our patients was similar to that of patients in previously reported series [1-6,17]. Clinically muscle-invasive malignancy accounted for 85.5% of the present cases. Our overall mean operating time for ileal conduits and the orthotopic ileal neobladder were comparable to those reported previously for ORC. Similarly, mean estimated blood loss and blood transfusion requirements were well within acceptable limits [1-6,17]. The mean hospital stay was only 6.1 days. Major and minor complications were 8% and 15.5%, respectively, which are comparable to standard published series from high-volume centers performing ORC. Perioperative mortality was 1.5%, which is less than other reports of 2% to 3% [1-6,17,19,20].

Histopathological results in the present study showed that TCC was the predominant histology. The mean number of lymph nodes removed was 17, with only 3 (1.5%) patients showing distal positive surgical margins. These outcomes confirm the meticulous surgical dissection of the procedure. Local recurrences in pelvic and distant metastases were recorded in only 16 (8%) and 9 (4.5%) patients, which are comparable to previously reported series on ORC [1,4,5,16,17]. At the median follow-up of 53.1 months, the 5-year overall survival, disease-free survival, and cancer-specific survival rates were 63.5%, 75.5%, and 71.5%, respectively. These rates are similar to those reported in studies with more patients [1,4,5,16,17]. On further analysis, we found that 5-year overall survival, disease-free survival, and cancer-specific survival rates were significantly higher in patients with organ-confined cancer and negative lymph nodes. This highlights the prognostic significance of these variables.

Due to strict attention to perioperative details, meticulous surgery, and a team-oriented surgical and postoperative approach, we have performed ORC with acceptable morbidity, decreased mortality, and favorable 5-year oncological outcomes that are similar to those reported from high-volume centers [1,4,5,16,17]. These outcomes can be considered as benchmarks against which minimally invasive procedures like LRC and RRC can be compared. Prospective randomized series involving a larger number of patients comparing ORC and LRC or RRC are needed in order to establish the long-term oncological efficacy of these procedures.

CONCLUSIONS

Radical cystectomy performed using an open approach has an acceptable perioperative morbidity and mortality and favorable 5-year oncological efficacy. Minimally invasive techniques need long-term prospective comparison with this approach before they can be accepted as a standard treatment for urinary bladder malignancy.

Conflict of Interest: none declared

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