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## Perioperative outcomes after open radical cystectomy for muscle invasive bladder cancer

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### Abstract

**Introductions:** Radical cystectomy with bilateral pelvic lymphadenectomy is a primary intervention for muscle invasive or refractory, high grade Ta, T1, Tis bladder cancer. Owing to its major undertaking, patient succumbs to infection and various morbidities. This study was to assess the perioperative outcomes and complications of radical cystectomy.

**Methods:** This retrospective study analyzed the perioperative outcome (early mortality within 30 days, length of stay, requirement of blood transfusion) of radical cystectomy in patients with bladder cancer during four years at Patan Hospital, Patan Academy of Health Sciences, Lalitpur, Nepal. Ethical approval was obtained. Study variables included patient's demographics, presenting symptoms, tumor types and configuration, need for blood transfusion, length of surgery, pathological stages, types of urinary diversions, hospital stay, early (<30 days) and late (31-90 days) morbidity and mortality.

**Results:** Total 32 patients underwent radical cystectomy. Data analysed on 18 patients, mean age was 66.7 years and painless hematuria 17 (94.4%). All were transitional cell carcinoma, high grade lesion in 17 (94.4%). Overall 6 (33.3%) patients developed early postoperative complications, paralytic ileus and prolong lymph drainage in 5 (27.8%), wound dehiscence in 4 (22.2%) and ureteric catheter dislodgement in two. There were 2 (11.1% of 18) mortalities (the mortality audit showed total 5 (15.6%) out of 32 radical cystectomy during the study period.

**Conclusions:** Perioperative complications occurred in 1/3rd following radical cystectomy for muscle invasive bladder, more complications in those with preoperative associated co-morbidities.

**Keywords:** bladder cancer, radical cystectomy, perioperative complications

## Introductions

Bladder cancer is the sixth most common cancer worldwide.<sup>1</sup> It is 5th common cancer in male in Nepal.<sup>2</sup> Radical cystectomy, pelvic lymph node dissection and urinary diversion is the gold standard treatment for muscle invasive bladder cancer (MIBC) and selected high-risk non-MIBC.<sup>3</sup> Despite refinements in surgical techniques and anesthesia, perioperative morbidity remains a challenge as patients are relatively elderly with multiple comorbidities.<sup>4</sup> Left alone or insufficiently treated, MIBC has high morbidity due to local and systemic progression, repeated hospitalizations and death.

American Society of Anaesthesiology (ASA) score, carcinoma in-situ and tumor stages are some of the predictors for increased rate and severity of early complications after radical cystectomy.<sup>5</sup> Open radical cystectomy without selecting favorable patient group has accepted morbidity, mortality, median length of stay of less than a week and an estimated blood loss of approximately 2-units.<sup>6</sup> Despite technological advances perioperative morbidity has remained stable at 11 to 68%.<sup>7</sup> In this 4-years single center review we aim to analyse the perioperative outcome of radical cystectomy for MIBC in local scenario, which will provide information that may serve the basis for future interventions to reduce the morbidities and complications of radical cystectomy in future.

## Methods

This study includes patients who had radical cystectomy for MIBC during 4 years period from March 2015 to February 2019 at Patan Hospital, Patan Academy of Health Sciences (PAHS), Nepal. Ethical approval was obtained from institutional review committee, IRC-PAHS.

In-patient identification numbers of patients who had radical cystectomy for bladder cancer were searched from operation room register. The files were retrieved from the hospital

record section for data analysis. Variables analysed were patient demographics (sex, age), presenting symptoms (painless hematuria, irritative bladder symptoms and history of smoking), ASA grade with known concomitant co-morbidities (hypertension, diabetes, COPD, heart disease), tumor types configuration and pathological stage, length of surgery, types of urinary diversions, estimated blood loss and need for blood transfusion, post-operative complications (paralytic ileus, lymphorrhea, respiratory problems, small bowel obstruction, anastomotic leak), adjunctive procedures to control complications, days of hospital stay and early within 30 days and late 31 to 90 days morbidity mortality.

Inoperable (surgeon's decision during intra-operative period), those treated with modality other than radical cystectomy, incomplete data or patients case file not available from hospital record section were excluded from analysis. The mortality was calculated both in patients whose record files were available and also the overall mortality out of total radical cystectomy during the study period from monthly morbidity- mortality audit system in the surgery department.

The SPSS version 16 was used for descriptive analysis.

### Working definitions-

- Intraoperative hemorrhage: hematocrit fall calculated by the difference in value soon after surgery and preoperative value.
- Sepsis: postoperative fever (temperature more than 38 or less than 36°C), pulse more than 100/minute, respiratory rate more than 20/minute, total leukocyte count more than 12000/mm<sup>3</sup> or less than 4000/mm<sup>3</sup>.
- Prolong length of stay: hospital stay more than 2-weeks after surgery.
- Prolong lymphorrhea: drainage of lymph from abdominal drain for more than two weeks.
- Paralytic ileus: postoperative vomiting associated with abdominal distension until postoperative day-5, lack of bowel activity

without signs of small bowel obstruction and cessation of oral intake or need of nasogastric decompression.

- Acute respiratory distress: severe respiratory insufficiency requiring unplanned intubation and assisted respiration.
- Wound dehiscence: wound breakdown with disruption of fascial suture requiring surgical repair.
- Pelvic lymph node dissection: standard template of the anatomic boundaries includes genitofemoral nerves laterally, the internal iliac artery medially, Cooper ligament inferiorly, and the point at which the ureter crosses the common iliac artery superiorly. Lymph nodes within the boundaries of internal iliac, external iliac, obturator, and presacral are removed.
- Early perioperative complications: adverse event within 30 days of surgery.
- Perioperative mortality: death from any cause within 30 days of surgery.
- Late complications: complication noted more than 31-90 days after surgery
- Definitions of concomitant comorbidities:
  1. Hypertension: stage-1 hypertension or above (ASA classification)<sup>9</sup> with at least one antihypertensive drug for more than 3 months.
  2. Diabetes: on treatment with oral anti-hyperglycemic agent or insulin.
  3. Coronary heart disease: with coronary stents or history of coronary artery bypass or myocardial infarction, or two episodes of angina pectoris with long-term medication with at least one specific drug (nitroglycerin, beta blockers, calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors).
  4. Chronic obstructive pulmonary disease (COPD): confirmed by spirometry, on long-term medication with bronchodilators and/ or corticosteroids.

At our center, radical cystectomy is performed with curative intent by standard technique under general anesthesia together with placement of epidural catheter, central line,

routine prophylactic antibiotics (inj. durataz & inj. metronidazole) and Foley's catheterization. Patient is put in supine position bed flexed 15 degrees at the level of anterior superior iliac spine to facilitate access to the deeper abdominal structure through lower midline incision. Surgical dissection includes, in male- cystoprostatectomy including prostate, seminal vesicles; in female- cystectomy together with removal of uterus, adnexa, anterior vaginal wall and urethra. Pelvic lymphadenectomy is carried out as per standard template dissection of lymph nodes.

For ileal conduit, uretero-enteric mucosa to mucosa anastomosis in single layer was performed in continuous pattern with polyglactin 5-0 (Bricker's type in 16 patients and Wallace type in 2 patients) over 6 Fr ureteric catheter, followed by end to end ileo-ileal anastomosis in single layer extra-mucosal interrupted fashion with polyglactin 3-0 suture. The distal end of ileal conduit is brought out as stoma at right lower abdomen.

For orthotopic neobladder, Studer's pouch was considered. To construct the reservoir, a 45-50 cm ileal segment was isolated about 20-25 cm proximal to the ileocecal valve. About 30-35 cm of the distal ileal segment is then de-tubularized on the antimesenteric border, leaving the proximal 15 cm intact for later implantation of the ureters. To construct the reservoir, the adjacent de-tubularized limbs are folded into a U shape, and the back wall were over-sewn. The bottom of the U was folded over between the two ends of the U, resulting in a roughly spherical shape reservoir consisting of four cross-folded ileal segments.<sup>9</sup> The ureters were next anastomosed to the afferent tubular segment in end-to-side refluxing fashion. Finally, the reservoir was anastomosed to native urethra,

Our routine protocol for symptomatic management of complications include high flow oxygen, antibiotics and chest physiotherapy in incentive care unit for pneumonia and acute respiratory distress; intravenous fluids, nil per oral and prokinetics for paralytic ileus; fluid and nutrition

supplementation and drainage for lymphorrhea; revision laparotomy with tension suturing for abdominal wound dehiscence; dressings and broad spectrum antibiotics for surgical site infection (SSI); laparotomy for small bowel obstruction not relieved by conservative management.

In order to diagnose possible urinary leak from abdominal drain, we opt to measure drain fluid to serum creatinine ratio. A ratio of more than 10 is considered urinary leak. Ureteric catheters are routinely removed at 1-week of surgery. Followup is done routinely in outpatient surgical referral clinic by consultant urologist at 2, 4 and 12 weeks after discharge from hospital.

**Results**

Out of total of 32 radical cystectomy performed during the four years study period, data on 18 patients were analysed after excluding 14 with incomplete data or whose files were not available. Out of 18 patients, 17 (94.4%) were males and 1 (5.6%) was female. The mean age was 66.67 years. Painless hematuria was present in 17 (94.4%), irritative symptoms in 11 (61.1%) and history of smoking in 13 (72.2%) of the patients. Thirteen (72.2%) of the patients were in ASA grade-2 with 1/4<sup>th</sup> having known concomitant co-morbidities of hypertension, followed by diabetes and COPD, Table 1.

**Table 1. Prevalence of the most frequent known concomitant co-morbidities in bladder cancer patients who had radical cystectomy (N=18)**

Comorbidities	N	%*
Hypertension	4	22.2
Diabetes	3	16.6
COPD	3	16.6
Heart disease	1	5.5
Anemia	9	50.0

\*total % adds up to more than 100 because of more than one co-morbidities in one patient

**Table 2. Local tumor (T) stages after final histopathology examination of radical cystectomy for bladder cancer (N=18)**

T	N	%
T1	5	27.8
T2	11	61.1
T2b	1	5.5
T4	1	5.5

**Table 3. Early complications within 30 days after radical cystectomy (N=18) for bladder cancer**

Perioperative complications (<30 days)	N	%
<b>Medical</b>		
Pneumonia	4	22.2
Acute respiratory distress	3	16.6
Atrial fibrillation	1	5.5
Cardio respiratory arrest	1	5.5
<b>Surgical</b>		
Paralytic ileus	5	27.7
Prolong lymph drainage (lymphorrhea)	5	27.7
Wound dehiscence	4	22.2
Surgical site infection (SSI)	3	16.6
Anastomotic dehiscence	2	11.1
Ureteric catheter dislodgement	2	11.1
Massive intraoperative bleeding	1	11.1
Small bowel obstruction	1	5.5

**Table 4. Late postoperative complications 31-90 days after radical cystectomy (N=18) for bladder cancer**

Late postoperative complications (>30 days)	N	%
Peristomal irritation	2	11.1
Incisional hernia	1	5.5
Uretero-enteric anastomosis stricture	1	5.5
Enteric fistula	1	5.5
Stress incontinence	1	5.5

All patients had transitional cell carcinoma, 17 (94.4%) high grade lesions. Five (27.7%) were T1 lesions, 11 (61.1%) T2 and one each T3 and T4. Four (22.2%) patients had positive lymph nodes. Multiple lesions were present in 12 (66.7%), papillary 7 (38.9%) followed by solid tumor in 6 (33.3%). One patient had urethral invasion seen on preoperative transurethral (TUR) specimen. Primary tumors accounted for 11 (61.1%) of the cases, while recurrences were recurrent.

Neoadjuvant radiation therapy was given to two patients and chemotherapy in three. Ten (55.6%) patients received Mitomycin C and one received Bacillus Calmette-Guerin (BCG) intravesical therapy after initial transurethral resection of bladder tumor (TURBT), refractory to BCG.

Mean operative time was 402.4±60.2 minutes, postoperative hematocrit drop 8.28% and blood transfusion in 14 (78%).

Urinary diversion was performed with ileal conduits in 17 (94.4%) and Studer's pouch (ileal neobladder) in 1 (5.55%). One patient with urethral invasion underwent urethrectomy. Histologically 11 (61.1%) were T2 lesions, Table 2. In four patients with T2b stage, lymph nodes were histologically positive.

Hospital stay was 19.2±5.8 days (median 16). Longer hospital stay was seen in those who had complications 26.1±10.3 days (median 21).

Early complications of paralytic ileus, lymphorrhea occurred in 1/4<sup>th</sup> of patients followed by wound dehiscence, and pneumonia in 5 (27.7%), Table 3.

Ureteric catheter dislodgement occurred in 2 (11.1%) of the patients on the first postoperative day, both during replacement of urostomy bag and no significant urinary leak was observed in the abdominal drain following the dislodgement, as drain to urinary creatinine ratio was below 10:1.

There were 2 (11.1%) postoperative mortalities among 18 cases analysed, however there were total 5 (15.6%) mortalities out of 32 cases as per morbidity-mortality audit record in the department.

The same morbidity-mortality reporting system also helped us to find out the exact cause of death in all the cases. Two were secondary to bowel complication due to anastomotic dehiscence, one each secondary to respiratory complication of pneumonia and intraoperative bleeding and cardiorespiratory arrest respectively. Arrest occurred during extubation phase of anaesthesia, however exact cause was not identified.

## Discussions

Overall early postoperative morbidities in our study were seen in 6 (33.3%), comparable to other larger studies reporting early complication of 38.6%<sup>8</sup> in 452 and 33%<sup>10</sup> in 70 patients. However, there is currently no standardized way to define complications or compare complication rates within the urological literature and radical cystectomy itself is considered to have major impact on these patients during lengthy surgical procedures.<sup>10</sup> Patients with MIBC are usually elderly. The average age of patients in our series was 66.7 years (range 53-77) and 13 (72.2%) were in ASA grade-2 with various

associated comorbidities. While improved patient selection and early detection could potentially reduce these rates, it is unlikely that significant reductions will be realized in the foreseeable future with similar operative due to old age of patients and requiring extensive surgical dissection and reconstruction.

Intraoperative and or postoperative blood transfusion was required in 14 (78%) of our patients, while others series report lower transfusion rate ranging between 39 and 65%.<sup>11,12</sup> In the study of 553 patients of radical cystectomy, 210 (38%) received blood transfusion either during surgery or in early postoperative period.<sup>13</sup> Preoperative anemia, high estimated blood loss, older age, non-organ confined disease, ileal conduit urinary diversion are the potential factors to dictate blood transfusion.<sup>13</sup> The relatively high transfusion rate in our series may be due to these well-known factors, plus preoperative anemia in 50% of the patients; ileal conduit urinary diversion in 94.4% and postoperative hematocrit drop of 8.3%. Besides these, intraoperative transfusion in our category of patients was to maintain bodily homeostasis and avoid eventual anastomotic break down due to intraoperative hypotension (iatrogenic) or hypovolemia.

The median hospital stay in our series was 16 days, longer than 6 days in a larger series of 553 patients.<sup>13</sup> The relatively prolonged hospital stay in our study may be due to the complications of prolonged ileus; anastomotic leak and wound dehiscence. Other possible reason could be our patients do not prefer to get discharged early owing to generally poor socioeconomic status of our population, poor transport facilities and non-existent community nurses for postoperative care. However, could not specifically looked into these factors owing to retrospective analysis. The average hospital stay after radical cystectomy in the literature ranges between 7 and 34 days.<sup>10</sup> Much shorter hospital stays is seen in the US as compared to European countries.<sup>14</sup>

One of the most common postoperative complications after radical cystectomy with urinary diversion is paralytic ileus. The ileus rate in our series was 27.7% compared to reports of as low as 8.6% in the literature.<sup>8</sup> Ileus result from the stress of surgery, which causes generalized sympathetic stimulation and could initiate a spinal reflex arc that impairs gastrointestinal motility. Despite early ambulation, prokinetics, and early feeding, we had increased rate of ileus. It probably was due to opiates analgesics and neurogenic comorbidity like diabetes and hypertension in some of our patients.

Higher ASA-grade, advanced age and comorbidities are possible risk factors for complications. Among 18 patients in our series, 13 (72.2%) were in ASA grade-2 with various concomitant co-morbidities of hypertension seen in 4 (22.2%), diabetes in 3 (16.6%), COPD 3 (16.6%), and heart disease 1 (5.5%). In literature the reported independent risk factors for postoperative morbidities are age and ASA grade >3.<sup>15</sup> Similarly, age and cardiac disease are also independent risk factor for postoperative complication.<sup>16</sup> In a prospective study, patients of ASA 3 or more were found susceptible to complications.<sup>17</sup>

There were altogether 5 (15.6%) mortality in our study when all the 32 cases were taken into consideration. Mortality figures were retrieved from our monthly departmental audit data. Reported mortality rates after radical cystectomy range between 0 and 9.5%, depending on the size of the series and the defined postoperative period.<sup>18,19</sup> A 12.7%, 90-day overall mortality was reported in 2011 reaffirming that radical cystectomy is safe in high risk elderly patients.<sup>20</sup>

We have certain limitations in our study like the limitations inherent to retrospective analysis, small sample size and relatively underutilization of neoadjuvant therapy in our patients compared to current recommendations that may influence outcome. Prime reason to avoid neoadjuvant chemotherapy in our patients was anxiety and fear of the bad prognosis owing to delay in

cancer surgery. However, our data represents acceptable overall outcome of radical cystectomy for MIBC performed at low volume center in a low income country.

## Conclusions

Our study reflects the outcome of radical cystectomy and pelvic lymphadectomy for muscle invasive bladder cancer had acceptable perioperative morbidities and mortality, in elderly patients with associated comorbidities.

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