Multimodal Perioperative Plan for Radical Cystectomy and Intestinal Urinary Diversion. I. Effect on Recovery of Intestinal Function and Occurrence of Complications

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OBJECTIVES
To discuss a multimodal perioperative plan aimed at reducing postoperative ileus and complications associated with radical cystectomy and urinary reconstruction.

METHODS
The protocol consisted of preoperative, intraoperative, and postoperative measures. The clinical parameters assessed were the time to the return of bowel movements, the presence and duration of postoperative ileus, the presence and duration of an intolerance to oral feeding, the interval to re-institution of a regular diet, and complications. The biochemical parameters (serum total protein and albumin levels and lymphocyte counts) were also assessed. A sample of 40 patients treated before the implementation of this protocol was included for comparison.

RESULTS
A total of 71 patients, mean age 74 years and American Society of Anesthesiologists status 2 and 3, consecutively underwent radical surgery for bladder cancer and were evaluable for results and complications. Urinary diversion was a heterotopic neobladder in 27 patients (38%), orthotopic in 23 (32.3%), and an ileal conduit in 21 (29.5%). bowel movements returned after a median of 2 days (range 1 to 6), intolerance to oral feeding was observed in 17 (23.9%) of 71 patients, and the median time to re-institution of a regular diet was 4 days (range 3 to 9). The complication rate was 26.7%, and the mortality rate was 4.2%. No effects were observed on postoperative protein depletion. In the historical group, the median time to diet resumption was 8 days (range 7 to 12).

CONCLUSIONS
A short time to the resumption of normal intestinal function and a low incidence of postoperative ileus after cystectomy was observed. However, the incidence of postoperative protein depletion was unaffected. Additional studies should address this subject.


Radical cystectomy represents the standard treatment for muscle-infiltrating bladder cancer and recurrent, high-grade, superficial transitional cell carcinoma not controlled by conventional therapy. It is recognized as a major operative procedure that carries the potential for serious complications. Intestinal urinary reconstruction generally follows cystectomy, with a consequent increase in the burden of the procedure; hence, attentive perioperative management is critical. Bladder cancer is predominantly a disease of the aging population, with a peaking incidence in the seventh decade when comorbid conditions are frequently present (eg, coronary artery disease, atherosclerosis, and cerebrovascular accidents), further emphasizing the importance of perioperative and surgical management. The mortality and morbidity inherent to the procedure are expectedly high and, although advances in perioperative medical care, anesthetic management, and surgical techniques have lowered mortality to less than 3%, the early postoperative morbidity rate (ie, within 30 days) exceeds 30%. Greater mortality and morbidity are observed in the elderly. Also, postoperative complications result in prolonged hospitalization. A delayed return of bowel function attributable to postoperative ileus (POI) stands out as one of the most frequent causes of increased length of stay (LOS), in abdominal general surgery series and radical cystectomy series. In recent years, there has been interest from various sources in the use of standardized healthcare strategies in an attempt to reduce variation, improve quality of care, and decrease the LOS for major surgical and urologic procedures. In the present study, we tested the hypothesis that an evidence-based protocol of perioperative management could contribute to preventing or reducing POI and the com-
plications associated with radical cystectomy and intestinal urinary diversion. We have reviewed the rationale, results, and complications of such a protocol.

MATERIAL AND METHODS

Candidates to radical cystectomy for bladder cancer with curative intent and intestinal urinary reconstruction (orthotopic or heterotopic neobladders, ileal conduits) were enrolled in this study. Neoadjuvant systemic chemotherapy was not administered in this study. Our plan consisted of preoperative, intraoperative, and postoperative measures, as previously described,18 and discussed here in detail.

Preoperative Measures

Mechanical bowel preparation was limited to administering cleansing enemas the afternoon before surgery. The patients were allowed to have a light dinner the evening before surgery, with fasting started at midnight. A central venous line was inserted, and an epidural catheter was placed, at the thoracic vertebral level, T10 or T11.

Intraoperative Measures

Administration of second-generation cephalosporins was started on the morning of surgery, renewed after the first 2 hours of the procedure, and maintained until removal of the surgical drains. Combined general and epidural anesthesia was given. Controlled hypotension was obtained by epidural blockade to help control blood loss. Judicious surgical dissection was facilitated by optical magnification (frontal loupes ×3.5), bipolar scissors, and hemoclips. Hypovolemia is associated with the risk of POI4,5 and was actively prevented by timely reintegration after exenteration (colloids or blood transfusions, or both) if blood loss exceeded 10% of the estimated whole blood volume. Adequate peripheral oxygen tension was maintained by ventilation, and hypothermia was prevented by upper body, air-warmed huggers. At the end of the surgical procedure, a jejunostomy cannula was placed in candidates for the artificial nutrition trial.

Postoperative Measures

The nasogastric tube (NGT) was removed shortly after the procedure (2 to 8 hours), and parenteral nutrition was started that evening. Parenteral nutrition provided 25 to 30 kcal/kg, at an 84 mL/hr infusion rate through a central venous line. Enteral nutrition consisted of the delivery of immunonutrients (Impact, Novartis, Munich, Germany) and was started on postoperative day 1 at a rate of 21 mL/hr; the parenteral infusion rate was decreased to 63 mL/hr. On postoperative day 2, enteral feeding was advanced to 42 mL/hr, and parenteral nutrition was decreased to 42 mL/hr. These rates of administration were maintained until oral feeding was well tolerated. In the presence of abdominal bloating, discomfort, or pain from bowel distension, the following measures were adopted sequentially and recorded: administration of prokinetic agents, a 50% reduction in the enteral infusion rate, or temporary interruption. After postoperative day 1, the oral intake of fluids and small amounts of soft food was allowed on demand. Postoperative pain control was obtained by injecting local anesthetic drugs by way of the epidural catheter at an infusion rate of 5 mL/hr and was maintained for 50 hours. Both active and passive mobilization was started on postoperative day 1.

Study Endpoints

The duration of POI (ie, absence of any bowel activity), interval to recovery of bowel sounds, interval to first passage of flatus, presence of intolerance to oral feeding (inability to tolerate oral diet after NGT removal), and interval to the resumption of reliable oral feeding (at least 1200 calories) constituted the study endpoints. In addition, standard biochemical parameters (ie, total protein and serum albumin levels and complete blood counts, including lymphocytes) were assessed preoperatively and repeated on postoperative days 1, 3, and 5 and on discharge. The effects of early artificial nutrition were tested in a two-stage Phase II trial. A detailed description of the study and the results and complications are addressed specifically in part II of this report.19

The complications were divided into the following subgroups: major medical complications (eg, myocardial infarction, cerebrovascular accident, pulmonary embolism, sepsis, pneumonia, or respiratory failure), major surgical complications (eg, any complication leading to repeat laparotomy), minor medical complications (eg, ileus, delirium, deep venous thrombosis, acute renal failure, acute pyelonephritis, hydropneumphosis, Clostridium difficile colitis), and minor surgical complications (eg, wound infection).

Retrospective Data

The medical records of a group of 40 consecutive patients who underwent radical cystectomy and intestinal urinary diversions before the adoption of our multimodal plan were evaluated retrospectively. The incidence and duration of POI, interval to the removal of NGT suction, interval to normal oral feeding, and the LOS were abstracted, as were the demographics, pathologic stage, diversion type, American Society of Anesthesiologists (ASA) category, operative time, and intensive care unit stay.

RESULTS

From December 2002 to December 2005, a total of 101 consecutive patients underwent radical cystectomy with pelvic lymphadenectomy at our institution. The protocol was not applied to 24 patients whose urinary diversion was ureterocutaneostomy or to 6 other patients because of unsuccessful positioning of the epidural catheter. Therefore, 71 patients were enrolled into the study and were evaluable for an analysis of the results and complications. The patients’ demographics data, ASA category, pathologic stage, diversion type, American Society of Anesthesiologists (ASA) category, operative time, and admission to an intensive care unit stay are shown in Table 1.

The median time to the return of peristalsis and flatus was 2 days (range 1 to 6). Intolerance to oral feeding was experienced by 17 (23.9%) of 71 patients, 9 of whom required reinsertion of an NGT. The median time to regular diet resumption was 4 days (range 3 to 9; Fig. 1). POI after the fourth postoperative day was observed in 16 patients (22.5%). The median preoperative basal and discharge values of serum total protein, albumin, and lymphocyte counts are given in Table 2.
Overall, 19 patients (26.7%) experienced complications. Major medical complications were observed in 5 patients (7%), including myocardial infarction in 4, which was fatal in 3, and severe sepsis in 1. Within the first 30 days, 3 (4.2%) of 71 patients died. Major surgical complications were observed in 8 patients (12.2%) and included intestinal fistula in 2, dislodgement of the jejunostomy catheter in 1, inadvertent stab wound of the jejunum in 1, small bowel intussusception in 1, and dehiscence of the abdominal fascia in 3. Minor medical complications were observed in 6 patients (8.4%) and consisted of delirium in 3, *Clostridium difficile* colitis in 2, and hydronephrosis in 1.

The median LOS for the entire group of patients was 15 days (mean 18.8, range 6 to 46).

**Retrospective Data**

The abstracted data of 40 consecutive patients (median age 70 years), who underwent radical cystectomy, from June 1999 to May 2002, are detailed in Table 1, and the clinical parameters in Table 2.

**COMMENT**

Radical cystectomy with urinary diversion is a procedure in which a reduction of morbidity, quick postoperative rehabilitation, limited LOS, and cost containment are difficult to achieve. POI has been identified as the most common cause of delayed recovery and protracted LOS. Therefore, a reduction in POI and early reinstitution of effective oral feeding are the key issues in decreasing hospitalization. Our multimodal perioperative protocol was aimed at reducing the interval to recovery and convalescence by focusing on bowel function as one of the main causes of patient discomfort and delay of recovery.

Traditionally, mechanical bowel preparation has been routinely recommended for patients undergoing radical cystectomy and urinary reconstruction. However, a meta-analysis performed to test the hypothesis that mechanical bowel preparation reduces the incidence of postoperative complications showed no differences in primary outcomes (ie, mortality, peritonitis, reoperation, and wound infections). Consequently, it was abolished in our protocol. Similarly, the practice of fasting before elective surgery has been recognized as unfounded. More liberal fasting is currently recommended by anesthesiologists. The reasons for administering combined anesthesia and analgesia, using both epidural and general anesthesia, included providing complete pain control, preventing POI and sustaining an optimal anabolic state. In addition, the thoracic catheter allows for continuous analgesia, from above the umbilicus to the deep pelvis, that can be maintained for the early postoperative period when effective analgesia is still needed. Although nasogastric decompression can be helpful intraoperatively, it has proved to be unnecessary and could increase the risk of pulmonary complications, as shown by a recent meta-analysis. Administering large amounts of fluids, especially saline (9 g/L sodium chloride), in the postoperative period can cause and prolong POI; therefore, saline was substituted with 5% dextrose.

The definition of POI has varied among studies. The interval to the return of peristalsis and the interval to the passage of first flatus are referred to as indicators; however, they have their own weaknesses. The small bowel recovers motility and absorptive function within hours...
after surgery. In contrast, gastric and colonic function can require 2 to 5 days.29,30 The detection of peristaltic movements can indicate small bowel activity; similarly, the presence of flatus can imply that the colon (ie, the left portion) has recovered. However, these signs do not mean that the digestive function is back to normal. Some patients can experience intolerance to oral feeding even in the presence of small bowel activity or passage of flatus. A coordinated, normal activity of the three bowel segments is required to restore efficient digestive function; therefore, we considered also the interval to regular diet resumption as a more appropriate clinical parameter to assess the duration of POI. Our protocol led to a short median time to regular diet resumption (ie, 4 days) in most patients. This is remarkably shorter than usual, as confirmed by the comparison with the retrospective data. It is difficult to identify the contribution of each measure; however, on the basis of published data, as well as ours, the use of epidural anesthesia and pain control and the control of hypovolemia and hypoxemia are likely to have the greatest effect.15,21,24 –26 Neither early reinstitution of a regular diet nor early enteral nutrition prevented postoperative protein depletion (ie, reduction of total protein, serum albumin, and lymphocyte count). This finding probably indicates that a longer time of exposure to nutrients is needed to restore protein synthesis after surgery. The median LOS was 15 days (mean 18.8). Chang and coworkers4 used a collaborative care pathway in a group of 304 patients with a median age of 64.9 years and mainly ASA categories 2 and 3. The investigators were able to discharge 74% of their patients 6 to 8 days after cystectomy. Using an approach similar to ours, Pruthi and coworkers17 applied a perioperative care plan to a group of 40 patients (median age 65 years). However, no details were given on their general health condition (ie, presence of comorbidities and ASA category). Their time to reinstitution of a regular diet (ie, 4.2 days) was also similar to ours, and they were able to discharge 70% of their patients after a mean time of 5.1 days. The reasons that may limit early discharge do not depend merely on surgical results. Other factors also play a role, including differences that are inherent to the national healthcare systems in the United States and Europe. In addition, the distance of a patient’s residence from a hospital, difficult access to intermediate caregivers and any form of nursing, and the absence of home healthcare arrangements, among others, are taken into account in the discharge decision process. Furthermore, recovering the capability to care for oneself might take some time—more than 5 to 8 days—in the elderly, and most of our patients would not accept being discharged before they were fully self-sufficient. A significantly longer median LOS among elderly patients is usually observed in the United States and the European community than for our elderly patients.3,7,8,11 Thus, because of the above-mentioned reasons, the efficacy of our plan is not reflected by the LOS of our study population.

The complications we observed are within the range reported by others (26.7%),1–11 and the mortality rate was 4.2%. Mortality and morbidity reflect the quality of medical assistance and patient selection. Our study population was composed of consecutive cases, nearly one half of the patients were aged 75 years or older, and one third were in ASA 3 category. In a recent review conducted within the National Surgical Quality Improvement Program, Hollembeck and coworkers,7 observed an overall morbidity rate of 30.5% in a large series of cystectomies, and the rate reached 38.5% among patients older than 70 years. Our findings also compare well with the findings of other series of similar patients.7–11 Two limitations of our study were the absence of a concurrent control group and the retrospective comparison with historical data abstracted from medical records. We acknowledge that a potential selection bias cannot be ruled out; furthermore, the differences in the results could

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Group</th>
<th>Historical Group</th>
</tr>
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<tbody>
<tr>
<td>Median time to bowel movements (days)</td>
<td>2 (1–6)</td>
<td>—</td>
</tr>
<tr>
<td>Median time to normal diet (days)</td>
<td>4 (3–9)</td>
<td>7 (7–11)</td>
</tr>
<tr>
<td>Intolerance to oral feeding</td>
<td>17/71</td>
<td>—</td>
</tr>
<tr>
<td>Postoperative ileus (beyond postoperative day 4)</td>
<td>16/71</td>
<td>15/40</td>
</tr>
<tr>
<td>Overall complications</td>
<td>19/71</td>
<td>9/40</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>15 (6–46)</td>
<td>22 (12–45)</td>
</tr>
</tbody>
</table>

Data in parentheses are ranges.

Table 2. Clinical and biochemical parameters

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Historical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein (g/dL)</td>
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<td></td>
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<tr>
<td>Basal</td>
<td>7.2 (4.1–8.6)</td>
<td>5.6 (4–7.2)</td>
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<tr>
<td>On day of discharge</td>
<td>4 (2.11–4.74)</td>
<td>2.9 (1.6–3.6)</td>
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<tr>
<td>Albumin (g/dL)</td>
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<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.88 (0.63–6.58)</td>
<td>1.63 (0.79–2.8)</td>
</tr>
<tr>
<td>On day of discharge</td>
<td>1.63 (0.79–2.8)</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Parameter</th>
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<td>Length of stay (days)</td>
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Data in parentheses are ranges.
reflect differences in both the management policy and the surgical technique. Randomized multi-institutional studies could test more objectively the validity and complications of perioperative care plans.

CONCLUSIONS

A short time to the restoration of normal intestinal function and a low incidence of POI after radical cystectomy and intestinal urinary reconstruction can be obtained in most patients by applying a perioperative management protocol with an evidence-based rationale. The postoperative protein depletion was unaffected, and the complication and mortality rates were acceptable in an aged population of patients with comorbidities. Refinements in perioperative management aimed at reducing the burden of radical cystectomy merit further investigation in randomized, multi-institutional studies.

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References