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ORIGINAL ARTICLE

Comparison of surgical stress response to laparoscopic and open radical cystectomy

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Abstract
Objectives To prospectively compare stress response to laparoscopic and open radical cystectomy by the measurement of humoral mediators and the incidence of systemic inflammatory response syndrome (SIRS).
Methods Thirty-eight patients undergoing radical cystectomy were prospectively assessed. Blood samples were obtained from all patients before surgery, during surgery, 72 h after surgery. Serum levels of interleukin (IL)-6 and interferon (IFN)-γ were measured using an enzyme-linked immunosorbent assay. We also investigated the incidence and duration of SIRS in the two groups.
Results The two groups had comparable perioperative variables except for less estimated blood loss in the laparoscopic group. The IL-6 levels increased during and after surgery in the two groups ($P < 0.001$). However, the IL-6 levels in the laparoscopic group were significantly lower than those in the open group during and after surgery ($P = 0.006$, $P < 0.001$). The incidence of SIRS was 57.1% in the laparoscopic group and 79.2% in the open group ($P = 0.149$). The mean duration of SIRS was 1.4 days in the laparoscopic group and 2.8 days in the open group ($P = 0.032$). The IFN-γ levels decreased, but there was no difference in the two groups over the entire period assessed. Multivariate analysis demonstrated that the group (laparoscopic versus open) was the only influencing factor on the levels of IL-6 and the duration of SIRS.
Conclusions Our study suggests that the laparoscopic group is markedly less stressful and it has a shorter duration of SIRS than the open group.

Keywords Bladder cancer · Laparoscopic radical cystectomy · Stress response

Abbreviations

LRC	Laparoscopic radical cystectomy
ORC	Open radical cystectomy
SIRS	Systemic inflammatory response syndrome

Introduction

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women in the USA, with an estimated 68,810 new cases and 14,070 deaths predicted for the year 2008[1]. Approximately 75–85% of patients with bladder cancer present with disease confined to the mucosa or submucosa and approximately 20% of patients present with invasive disease. Open radical cystectomy (ORC) is the standard treatment for recurrent high-risk superficial or invasive bladder cancer because it provides excellent local cancer control [2]. Since the introduction of laparoscopic radical cystectomy (LRC), LRC had been performed in an increasing number of centers [3–5]. The potential benefits of the laparoscopic approach include lower surgical blood loss, earlier return of bowel function, and more rapid postoperative convalescence [6, 7]. Therefore, LRC has been proposed to be less traumatic approach than open surgery.

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To date, no study has examined the extent of surgical trauma and the subsequent systemic response after LRC and ORC using quantifiable variables. Surgical trauma causes a local activation of various cells (e.g. monocytes and macrophages), which release cytokines and other mediators [8]. This activation is either limited to a local level or can be followed by a systemic acute-phase reaction. Experimental and clinical data suggest that the intensity of the acute-phase response is proportional to the extent of tissue damage [9]. The postoperative levels of proteins and interleukins (ILs) related to acute-phase response, e.g. tumor necrosis factor (TNF)-a, interferon (IFN)-γ, IL-1, IL-6, and IL-10, C-reactive protein, and systemic inflammatory response syndrome (SIRS), have been found to correlate with the magnitude of the surgery and the presence of complications. They have, therefore, been accepted as markers of tissue trauma after surgery [8, 10–12].

The aim of the present study was prospectively compare the surgical stress response to LRC and ORC by the measurement of humoral mediators and the incidence of SIRS.

Materials and Methods

From October 2006 and August 2008, 38 patients were included in the present study. Of these patients, 24 patients underwent ORC and fourteen patients underwent LRC (Table 1). The selection of laparoscopic vs open approach was based on the surgeon's discretion and the patient's overall health status. Patients with clinically localized bladder cancer without metastases were eligible to undergo LRC. Patients who could not tolerate the pneumoperitoneum or modified lithotomy position were excluded from the laparoscopic approach. In addition, patients with bulky tumors or locally advanced disease were referred for neoadjuvant chemotherapy, then open surgery would be chosen for these patients. Patients were provided written informed consent to surgery and to the use of their clinical data for the present study.

The technique for LRC has been previously described [13]. For an ileal conduit, the line between the second and fourth port was converted to a 7-cm incision. In the case of an orthotopic neobladder, a midline subumbilical skin incision was made for urinary diversion. All patients had undergone a pelvic lymphadenectomy laparoscopically or through the subumbilical incision. ORC was performed by a periumbilical midline incision in the traditional manner.

Postoperative management was similar in the two groups. All the clinical data for each patient were collected prospectively. The clinical variables included patient age, sex, American Society of Anesthesiologists (ASA) score, body mass index, the type of urinary diversion, tumor stage, operative time, intraoperative estimated blood loss, the time of bowel recovery, and the length of hospital stay. In patients undergoing LRC, the operative duration was calculated from the insertion of the Veress needle to the suture of the last laparoscopic port, whereas for ORC it was calculated from skin incision to suture.

Table 1 The clinical and pathological characteristics and incidence of SIRS in the two groups

	Laparoscopic group (n = 14)	Open group (n = 24)	P
Age ± SD (years)	63.7 ± 10.1	58.0 ± 11.2	0.096
Male/female ratio	13:1	23:1	1.000
Body mass index ± SD (kg/m^2)	22.1 ± 3.2	21.7 ± 2.7	0.722
ASA score	1.7 ± 0.6	1.8 ± 0.5	0.846
Urinary diversion			
Ileal conduit	12	21	1.000
Ileal neobladder	2	3	
Tumor stage			
T1	4	6	0.967
T2	6	12	
T3	3	4	
T4	1	2	
Operative time ± SD (min)	371.1 ± 56.7	336.9 ± 69.1	0.122
Estimated blood loss ± SD (cc)	250.0 ± 116.0	652.1 ± 262.7	<0.001
Time to oral intake ± SD (d)	3.7 ± 1.7	5.0 ± 2.4	0.095
Length of hospital stay ± SD (d)	19.6 ± 6.9	20.5 ± 9.7	0.867
Patients with SIRS (%)	8 (57.1)	19 (79.2)	0.149
Duration of SIRS ± SD (d)	1.4 ± 1.4	2.8 ± 1.9	0.032

ASA American Society of Anesthesiologists, *SIRS* systemic inflammatory response syndrome, *SD* standard deviations

SIRS was applied as an index to evaluate operative systemic response after surgery. The diagnosis of SIRS with reference to criteria determined in 1991 at the Consensus Conference of American College of Chest Physicians and Society of Critical Care Medicine should have two or more of the following conditions: body temperature of 38°C or greater or less than 36°C; heart rate greater than 90 beats per minute; respiratory rate greater than 20 breaths per minute or partial pressure of carbon dioxide in arterial gas less than 32 mmHg; or white blood cell count greater than 12,000 cells per mm^3 or less than 4,000 cells per mm^3, or immature band cell forms greater than 10% [14]. The duration of SIRS was calculated in days.

Blood samples were obtained from all patients before surgery, during surgery (completing radical cystectomy), 72 h after surgery. In each case, 5.0 ml of venous blood was aspirated; serum was separated by centrifugation,

Table 2 The median (IQR) levels of IL-6 and IFN-γ at the sampling times in the two groups

Variable/group	Preoperative	Intraoperative	Postoperative 3rd	*P*
IL-6 (pg/ml)				
LRC (range)	5.13 (2.30–10.91)	10.39 (3.74–14.78)	63.94 (26.34–95.48)	<0.001
ORC (range)	4.32 (2.10–13.33)	13.75 (3.29–22.61)*	130.50 (51.68–182.60)*	<0.001
IFN-γ (pg/ml)				
LRC (range)	10.12 (5.84–17.78)	8.57 (5.61–14.04)	6.70 (5.38–12.74)	<0.001
ORC (range)	11.24 (5.91–22.52)	9.44 (4.12–18.44)	7.81 (2.71–16.61)	<0.001

* $p < 0.001$ (compared with the matched value)

aliquoted, and stored at −70°C until required. As cytokines are generally unstable molecules, all specimens were collected and handled carefully using standardized conditions. Serum levels of IL-6 and IFN-γ were measured using an enzyme-linked immunosorbent assay (RapidBio Lab, California, USA). Tests were performed according to the manufacturers' instructions.

Parametric continuous variables are reported as the mean (SD), and the median and interquartile range (IQR) for nonparametric continuous variables. The Mann–Whitney *U*-test was used to compare the median values of two nonparametric variables and Student's *t*-test to compare the mean values of two independent parametric continuous variables. The Friedman test was used to compare the median values of IL-6 and IFN-γ. Pearson chi-square or Fisher's exact test was used to compare categorical variables. A multivariate, stepwise regression analysis was used to analyze all variables to determine the potential significance of a host of factors on the levels of IL-6 and the incidence of SIRS. The variables evaluated in this study included age, sex, body mass index, ASA score, the type of urinary diversion, tumor stage, operative time, estimated blood loss, postoperative ileus, and surgical group. A two-sided $P < 0.05$ was considered to indicate statistical significance.

Results

Table 1 summarizes the clinical and pathological data of the patients analyzed. The LRC and ORC groups had comparable variables before and after radical cystectomy, except for estimated blood loss, which was significantly higher in the ORC group ($P < 0.001$). Three patients in the laparoscopic group developed perioperative complications, including one ileus, one pneumonia, and one pelvic abscess. Ten patients in the open group presented complications, including seven ileus, two wound infections, and one wound dehiscence. All these patients in the two groups were managed conservatively, and no reoperation was necessary.

Table 3 Multivariate analysis of potential influencing factors on the levels of IL-6 after surgery

Variable	Categories	Standardized coefficients	*P*
Age (year)	<60/60–65/> 65	0.098	0.499
Sex	Male/female	0.051	0.680
Body mass index (kg/m^2)	<18.5/18.5–23/> 23	0.098	0.444
ASA score	1/2/3	−0.082	0.546
Urinary diversion	Ileal conduit/ileal neobladder	0.151	0.244
Tumor stage	$T_1/T_2/T_3/T_4$	0.205	0.101
Operative time (min)	<300/300–360/>360	−0.137	0.307
Estimated blood loss (cc)	<300,300–600, >600 ml	−0.056	0.736
Ileus	No/yes	0.166	0.215
Group	ORC/LRC	−0.802	<0.001

ASA American Society of Anesthesiologists, *ORC* Open radical cystectomy, *LRC* laparoscopic radical cystectomy, Ileus was defined as the lack of bowel activity beyond postoperative day 4

Table 2 showed the median levels of IL-6 and IFN-γ at the sampling times in the laparoscopic and open group. The baseline levels of IL-6 were comparable in both arms. The serum levels of IL-6 increased significantly during and after the operation in both groups, and the increase in IL-6 levels in the open group was significantly greater than that in the laparoscopic group during and after the operation ($P < 0.01$). The multivariate regression analysis revealed that the surgical group was the only influencing factor on the levels of IL-6 after surgery (Table 3). The levels of IFN-γ decreased during and after surgery in the two groups. However, the laparoscopic and open groups had similar serum concentrations of IFN-γ over the entire observation period ($P > 0.05$).

SIRS occurred in 27 patients in this study (71.1%). Although not statistically significant, the proportion of patients with SIRS tended to be smaller in the laparoscopic group than in the open group (57.1 vs. 79.2%, $P = 0.149$).

However, once SIRS developed, its duration was clearly shorter in the laparoscopic group than in the open group ($P = 0.032$). Multivariate regression analysis showed tumor stage and operative time were not independent influencing factors, only the surgical group was the influencing factor on the duration of SIRS after surgery ($P = 0.05$).

Discussion

Any surgical procedure impairs homeostasis and triggers various hemodynamic, metabolic, and immunologic reactions. Intensity of the disturbances observed in the postoperative period correlates with the degree of the tissue trauma. Results of many experimental and clinical studies have proved that surgical trauma is connected with the impaired immune response in the postoperative period [15]. This impairment can be connected with altered production of proinflammatory cytokines, as well as inhibition of cellular response [16]. The intensity of the acute-phase response is proportional to the extent of tissue damage [9]. Consequently, levels of proteins and interleukins related to acute-phase response, e.g. TNF-a, IL-1, IL-6, and IL-10, IFN-γ, C-reactive protein, and SIRS, have been used in several clinical studies as criteria to evaluate the tissue trauma [8, 10–12].

In our study the IL-6 levels had been statistically increased in the ORC compared with LRC, which reflected the lower tissue damage of LRC. These observations are similar to those obtained by Fracalanza et al., Miyake et al., and Ruzic et al., who studied laparoscopic and open surgery in urology [9, 10, 12]. In addition, the level of cytokine production may have therapeutic relevance. IL-6 has been shown to be a useful parameter for the prediction of postoperative complications and organ failure [17]. However, the present study did not show the IL-6 levels had any correlation of postoperative results.

Both IL-2 and IFN-γ encourage the development of the Th1 subset of lymphocytes and are responsible for cell mediated immunity [18]. Immunosuppression after major trauma results mainly from T-cell dysfunction and is characterized by impaired synthesis of IL-2 and IFN-γ [19]. Brune et al. reported that the decrease in IFN-γ production was significant after conventional cholecystectomy, but not after the laparoscopic operation by measuring cytokine secretion of isolated T-cells in vitro [20]. Fuji and associates demonstrated that the IFN-γ concentration was slightly increased postoperatively in patients undergoing laparoscopy-assisted distal gastrectomy, while it was depressed in the open gastrectomy group. However, the differences did not reach statistical significance until the 3rd postoperative day [21]. In our study, IFN-γ showed a significant decrease during and after surgery, but no difference was found in the two groups over the entire period assessed. These data suggest impaired Th1 function was similar in the LRC and ORC group, and the main reason was probably that radical cystectomy with urinary diversion itself was a challenging surgery whether by open or laparoscopic surgery.

SIRS is defined as a nonspecific inflammatory response of the host against various stresses that cause generalized inflammation, and it is useful to evaluate the systemic responses of the host. SIRS is a parameter that reflects the real surgical invasiveness in patients. Kishino and colleagues concluded that the factors related to the surgical invasiveness evaluated by SIRS were operative time and a concurrent ventriculoperitoneal shunt during augmentation ileocystoplasty in patients with spina bifida [22]. When surgery does not produce severe complications, patients will not develop SIRS or the condition will improve spontaneously without any specific treatments within a few days postoperatively, even though they might temporarily develop SIRS. Haga et al. showed that SIRS was a useful parameter for the early detection of postoperative complications and end-organ dysfunction after gastrointestinal surgery [23].

Lang et al. demonstrated that retroperitoneoscopic adrenalectomy had a lower incidence of SIRS than open adrenalectomy for pheochromocytoma [24]. In our series, LRC group had a smaller proportion of patients with SIRS and also had a shorter duration than ORC group, which were consistent with Mutoh's results in the adrenalectomy. They showed that SIRS tended to be smaller and its duration was also shorter in the laparoscopic adrenalectomy than in the open one [12]. As a whole, the local trauma and systemic effect caused by LRC was less than by ORC in patients with bladder cancer. Multivariate analysis demonstrated that the group (laparoscopic versus open) was the only influencing factor on the levels of IL-6 ($P < 0.001$) and the duration of SIRS ($P = 0.05$) after surgery.

Despite lower surgical stress response to LRC that we were able to demonstrate, the design of our study entails a few problems that might limit the validity of our results. The study is a nonrandomized allocation of the patients to the study arms, and the few patients enrolled. As to the first point, the choice of surgical approach for radical cystectomy is based on the surgeon's discretion and the patient's health status, and very few patients are currently willing to undergo randomization to these two different surgical techniques. As no conclusive evidence show that LRC gives similar long-term outcomes than ORC, LRC remains investigational and patients with bulky tumors or locally advanced disease were referred for open surgery in our series. In addition, there were more minor complications in the ORC group than in the LRC group. So the results require validation in larger clinical studies.

In conclusion, our study suggests that LRC is markedly less stressful and it has a shorter duration of SIRS than

ORC. The data support the usefulness of LRC. Further examination into the association between tumor progression and immunological response after LRC is needed to clarify the immunological response after LRC and the usefulness of LRC for cancer surgery.

Conflict of interest statement We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work. There was no conflict of interest.

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