

Extra-Peritoneal versus Trans-Peritoneal Open Radical Cystectomy - Comparison of Two Techniques in Early Post-Operative Complications

Mohammad Soleimani¹, Ehsan Moradkhani², Navid Masoumi^{1*}, Jafar Gholivandan¹

Purpose: The conventional Trans-Peritoneal Radical Cystectomy (TPRC) harbors numerous postoperative complications, the most prevalent of which are Gastrointestinal (GI) problems. To reduce these morbidities we introduced our own version of extra-peritoneal approach and compared it with the conventional method.

Materials and Methods: In a cross-sectional observational retrospective design, eligible bladder cancer patients whom underwent Extra-Peritoneal Radical Cystectomy (EPRC) or TPRC in our center, were considered for this study and were compared for early post-operative complications.

Results: Ninety-nine patients in TPRC and 81 in EPRC were compared. The two techniques differed in their mean operation time (298.2 ± 37.8 min TPRC vs. 262.8 ± 37.2 min EPRC, $P : 0.001$). Early GI complications were lower in EPRC groups, including oral intake intolerance (21 vs. 8, $P : 0.04$), ileus (19 vs. 8, $P : 0.04$), intestinal obstruction (3 vs. 0, $P : 0.04$), and anastomosis leakage (8 vs. 1, $P : 0.01$). Urine leak (14 vs. 7, $P : 0.02$) and wound related complications (19 vs. 6, $P : 0.02$) also favored EPRC group.

Conclusion: The extra-peritoneal technique is beneficial in reducing postoperative morbidity, especially the more prevalent GI complications. This approach is functionally safe and allows preservation of the peritoneal integrity.

Keywords: bladder cancer; cystectomy; urinary diversion; postoperative complications

INTRODUCTION

Although Trans-Peritoneal Radical Cystectomy (TPRC) with pelvic lymphadenectomy is the standard technique in muscle invasive and high risk non-muscle invasive bladder cancer, its postoperative complications, ranging from pain to metabolic disturbances, makes it a difficult choice for the patient and even the surgeon⁽¹⁾. Given this, revising the traditional technique to lower postoperative morbidity is imperative.

In this regard, the Extra-Peritoneal (EP) approach was first introduced by Kulkarni in 1999⁽²⁾ and further along, slightly various modifications were introduced in other patient series⁽³⁻⁵⁾. This approach resulted in decreased postoperative complications.

Nevertheless, the best patients suitable for this technique are still a matter of debate and this is mostly due to paucity of studies, small number of included patients, and limited number of randomized trials. Additionally, the issue of oncologic efficacy and the danger of residual tumor cells is still not completely reinstated.

With these issues in mind, we designed this study to implement our technique with small modifications, to compare TP and EP approaches with regard to early postoperative (< 30 days) complications and patients' characteristics.

MATERIALS AND METHOD

Patients

In a cross-sectional observational retrospective design, all bladder cancer patients of a single clinician whom underwent radical cystectomy in our center, from April 2015 till January 2019, were considered for this study. All surgeries were done by the senior author. Before May 2017, cystectomies were performed with trans-peritoneal approach and after that it was changed to extra-peritoneal method and the results of these two methods were compared. Both ileal orthotopic and conduit diversions were included.

Altogether, our study population was 200 patients, 100 in each group, and their data were collected from their admission records, using a questionnaire. Our objective was to compare the complications in the early postoperative period (first 30 days) between the two groups. Length of surgery and hospital stay, amount of intraoperative bleeding and pack cell (PC) transfusion, perioperative complications (including pain, ileus, oral intake intolerance, urinary leak, anastomosis leak, intestinal obstruction, and wound related problems), oncological parameters (including surgical margin, histo-pathological stage and resected lymph nodes) and 30 day mortality rate were the study variables applied for comparison. Any patient with a previous history of extensive abdominal surgery, abdominal or pelvic radiotherapy,

¹Department of Urology, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences; Tehran/ Iran.

²Urology-Nephrology research center, Shahid Beheshti University of Medical Sciences; Tehran/ Iran.

*Correspondence: Address: Saadat Abad St., Shahid Modarres Hospital, Tehran/Iran.

Tel: +982122074087. Fax: +982122074101. Email: nmasoumig@gmail.com

Received April 2020 & Accepted August 2020

Table 1. Patients' clinical and pathological Characteristics.

	TPRC† group (N=99)		EPRC‡ Group (N=81)		P value	
	Conduit	Orthotopic	Conduit	Orthotopic		
Number (%)	69 (70)	30 (30)	56 (69)	25(31)	1.00	
Mean Age (years)	73.01 ± 9.7	63.4±7.4	68.89±10	64.52±8	0.00	
Sex	Male : 90 Female: 9		Male: 74 Female: 7		0.9	
Mean BMI~ (kg/m ²) ± SD	25.4 ± 3.36		25.15 ± 2.71		0.21	
Mean ASA* Score	1.6		1.5		0.27	
Prior abdominal surgery (%)	1 (1)		5 (6)		0.18	
Pathological Tumor category						
T0N0	1	0	2	2	0.31	
T1N0	24	10	18	9		
T1N1	0	2	7	3		
T2N0	26	11	16	8		
T2N1	11	2	8	2		
T3aN0	0	2	1	0		
T3aN1	6	2	1	1		
T3b N1	2	0	0	0		
T3aN2	0	0	1	0		
T4a N0	1	0	0	0		
T4a N1	0	1	0	0		
Positive surgical margin	2	0	0	0		0.19
Peritoneal involvement (stage)	1 (T4N0)	2 (T4N1-T3aN1)	1(T3aN2)	1(T3aN1)		0.2

†Trans-peritoneal Radical Cystectomy

‡Extra-peritoneal Radical Cystectomy

~ Body Mass Index

* American Society of Anesthesiologists' classification of physical health

or inflammatory bowel disease was excluded as it may impede peritoneal release. None of the patients had neo-adjuvant or systemic chemotherapy. Our ethics committee approved the design and all persons gave us their informed consent prior to inclusion in the study. Pain was measured by the mean amount of times patients ordered on demand morphine on postoperative days. Ileus was defined as oral intolerance with nausea, vomiting and abdominal distention which required holding oral intake and starting intravenous support. Oral intake intolerance was milder form of nausea after meal without distention which usually resolved with a brief period of food abstinence and gradual restart afterwards. Anastomosis leak was defined as bile-colored secretion from abdominal drain ± abdominal distention.

Preoperative Preparation

All patients underwent mechanical bowel preparation with 2-3 Li of Poly Ethylene Glycol (PEG) the day before surgery. They also received 1 dose of intravenous Ceftriaxon (1 gr) and Metronidazole (500 mg) and had only a liquid diet the day before surgery. Spiral pelvic computed tomography and abdominal ultrasonography were used for preoperative staging. All worn antithrombotic stockings before transferring to the operation room.

Surgical Technique

The technique for TPRC was the same as described by Hautmann⁽⁶⁾ and we followed the steps described by Kulkarni⁽²⁾ for the EPRC. In brief, for extra-peritoneal approach, after a median infra-umbilical incision and entering the space of Retzius, standard bilateral pelvic lymphadenectomy was performed; the boundaries were: genitofemoral nerve laterally, the internal iliac artery medially, cooper ligament caudally, and the crossing of the ureter at the common iliac artery cranially. The release of the prostate was accomplished as retro-pubic radical prostatectomy with care to preserve the neurovascular bundle in eligible patients and releasing the attachments of the denonvilliers' fascia off the rec-

tum. The dissection is continued cephalad, dividing the inferior and middle vesical vessels on either side until releasing the ureters 1 cm proximal to the uretero-vesical junction which was then ligated and cut alongside the vasa and ureteral tip was sent for frozen section. The remainder of the surgery for either dissecting the peritoneum off the bladder or removing the bladder with the overlying peritoneum was dependent on the location of the tumor inside the bladder and the feasibility of dissecting the peritoneum off the bladder dome. In case of dome or posterior bladder wall tumor or suspicious adherence of peritoneum to bladder, a circular window was made in the peritoneum at the level of the bladder dome and then cystectomy was completed by the cutting the urachus at the level of the umbilicus. The extremes of the peritoneal window were controlled by 2 Vicryl sutures, for preventing the over tearing and keeping the flaps available for later closing the peritoneal cavity. In the remainder of the patients, the peritoneum was dissected off the dome and urachus was cut at the level of umbilicus, superficial to the peritoneum, completing the cystectomy totally extra-peritoneally and only a small slit in peritoneum was opened to access the small intestine. With this technique, distal ureters needed limited dissection and they were implanted extra-peritoneally and in a refluxing manner to conduit or neobladder (**Figure 1**). At the end, peritoneal window was closed by stitching the peritoneum to the mesenteric pedicle (**Figure 2**). In female patients the genital organs were resected in all cases.

Post operation Management

Post operation management was the same for the 2 groups. Antithrombotic medication was started the morning after surgery. All patients were monitored in ICU on the first postoperative day and then transferred to the ward for the remainder of the post op period. All mobilized the day after surgery and Nasogastric (NG) tube was removed. Pain was controlled by IV Acetaminophen (Aptel®) 1 gr every 6 hours ± on demand 2.5 mg of intramuscular morphine. Liquid diet was com-

Table 2. Surgery related data in trans-peritoneal and extra-peritoneal cystectomy patients.

	TPRC† group (N=99)	EPRC‡ group (N=81)	P value
Length of surgery (min) (mean ± SD)	298.2 ± 37.8	262.8 ± 37.2	0.001
Postoperative hospital stay (days) (mean ± SD)	10.11 ± 5.78	8.72 ± 4.02	0.07
Intra-operative bleeding (Li) (mean)	1.31	1.63	0.1
Pack Cell transfusion~ (%)	Conduit: 13(13) Orthotopic: 11(11)	Conduit: 15(18) Orthotopic: 6(7)	0.14
Pain Medication			0.42
No morphin*	2	1	
1 dose of on-demand morphin*	2	2	
2 doses of on-demand morphin*	45	35	
3 doses of on-demand morphin*	49	43	
4 doses of on-demand morphin *	1	0	
Oral Intake intolerance (%)	Conduit: 9(9) Orthotopic: 12(12)	Conduit: 3(4) Orthotopic: 5(6)	0.04
Ileus after surgery (%)	Conduit: 9(9) Orthotopic: 10(10)	Conduit: 4(5) Orthotopic: 4(5)	0.04
Anastomosis Leak (%)	Conduit: 3(3) Orthotopic: 5(5)	Conduit: 1(1) Orthotopic: 0(0)	0.01
Urine Leak (%)	Conduit: 6(6) Orthotopic: 8(8)	Conduit: 3(4) Orthotopic: 4(5)	0.02
Obstruction (%)	Conduit: 1(1) Orthotopic: 2(2)	Conduit: 0(0) Orthotopic: 0(0)	0.04
Wound Infection(%)	19 (19)	6 (7)	0.02
Death (%)	2 (2)	1 (1)	0.1

†Trans-peritoneal Radical Cystectomy

‡Extra-peritoneal Radical Cystectomy

~ Number of patients received Pack cell transfusion

* Number of patients which requested doses of Morphine

menced on day 3 with gradual addition of solid food on day 5.

Statistical Analysis

We used SPSS V.25 program for statistical calculations. T and chi square tests were used for difference analysis between 2 groups. Mann-Whitney U test were utilized for non-normal distributions. *P* value < 0.05 was considered significant.

RESULTS

Of a total of 200 patient records, 20 were excluded (six previous abdominal surgeries and 14 Uretero-cutaneous diversions) and 180 patients were considered for analysis. Hundred and sixty-four (91.1%) of our participants were male and 16 (8.9%) were female. The mean age of our study population was 68.95 ± 9.93 (range: 37-88 years). The characteristics of enrolled patients are presented and compared in **Table 1**.

The mean operation time was shorter in EP method (262.8 ± 37.2 in EPRC vs. 298.2 ± 37.8 in TPRC, *p* = 0.001). However, there were no statistically significant difference in the mean post operation hospital stay, intra-operative bleeding and pain medication (Table 2). Detailed assessment of gastrointestinal complications

disclosed differences in oral intake intolerance (*p*: 0.04), ileus (*p*: 0.04), intestinal obstruction (*p*: 0.04) and anastomosis leak (0.01) in favor of EP group. Re-do surgery was required in two patients, due to intestinal obstruction and anastomosis leak, both of them in TP group. Urine leak was diagnosed in 14 (14%) TP and 7 (9%) EP patients, none of which required re-exploration. Wound related complications favored EPRC group with significant difference (*p*: 0.02). However, the type of diversion (conduit or orthotopic) did not affect wound complication rate. The post-operative complications using Clavien Dindo classification is presented in **Table 3**.

The most prevalent pathologic stage of the RC specimen was T2N0. The histologic subtype was TCC in all our patients and we didn't have any pure non-urothelial histologic group. Detailed descriptions of pathological stages are illustrated in Table 1. The most number of lymph nodes resected was 17 which was reported in 36 patients. The average number of resected lymph nodes per patient was 15.59 (range: 7-25) which disclosed no difference between the two groups (*P*: 0.07). Only 2 patients were margin positive and both were in TPRC group. No relation was observed between surgical mar-

Table 3. Surgery related complications in trans-peritoneal and extra-peritoneal cystectomy patients based on Clavien Dindo classification.

	TPRC† group (N=99)		EPRC‡ group (N=81)		Total	P value
	Conduit	Orthotopic	Conduit	Orthotopic		
Grade 1	9	10	4	4	27	0.03
Grade 2	6	8	3	4	21	0.02
Grade 3	1	2	0	0	3	0.04
Grade 4	0	0	0	0	0	-
Grade 5	1	1	0	1	3	0.7

†Trans-peritoneal Radical Cystectomy

‡Extra-peritoneal Radical Cystectomy

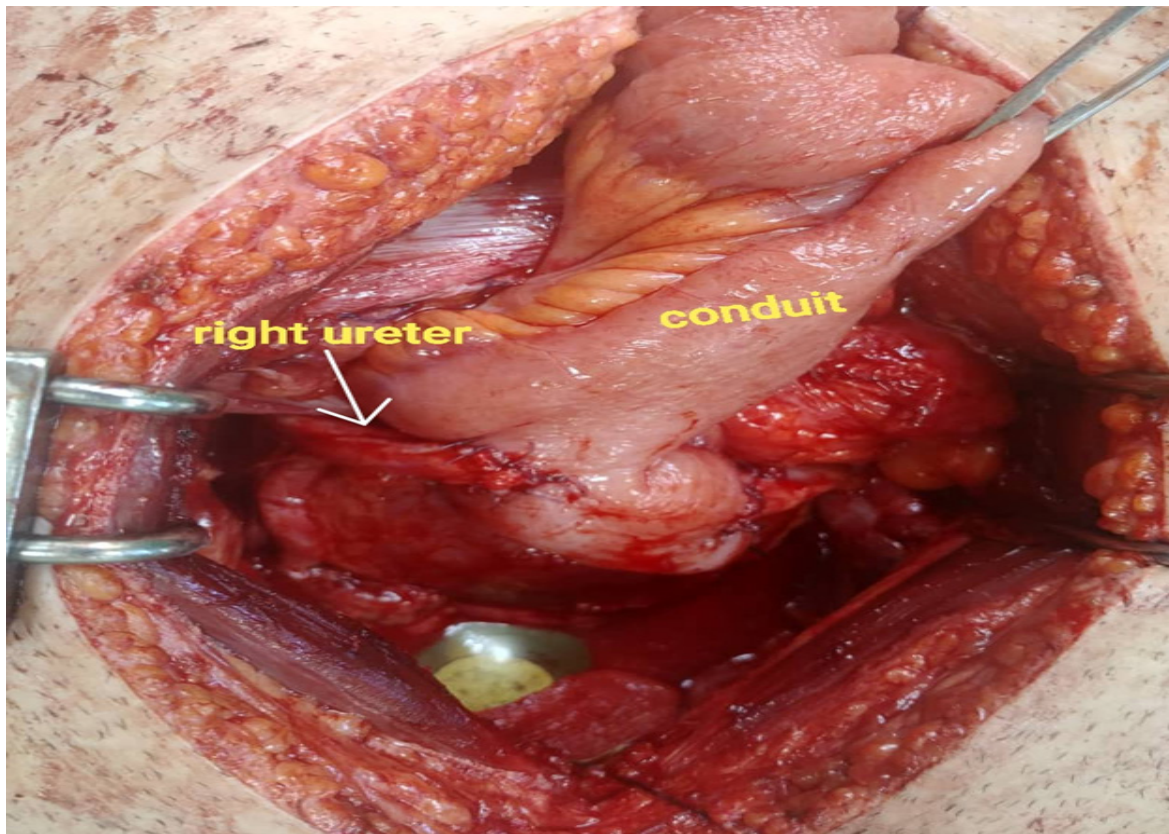


Figure 1. Extra-peritoneal implant of the right ureter to ileal conduit.

gin and method of surgery ($p : 0.19$). Five patients had peritoneal involvement in pathology report (3 in TPRC and 2 in EPRC group, Table 1) all of which were $>T2$ stage ($p : 0.2$). Three mortalities were reported in the 30 postoperative day which was due to massive pulmonary emboli (TP orthotopic), acute myocardial infarction (EP conduit), and septicemia due to intestinal leak (TP conduit).

DISCUSSION

Radical cystectomy with trans-peritoneal approach and antegrade bladder resection has a major drawback in violating the anatomical compartmentalization of peritoneal and retroperitoneal space⁽¹⁾. This translates into increased morbidity (16-66%) in the early 30 postoperative days^(7,8). Amongst which, the most frequent complication is gastrointestinal problems with nearly 29% of cystectomy patients affected⁽⁴⁾. A possible reason for this high rate is the contact of intestinal serosa with the de-peritonealized pelvic wall. This induces an inflammatory reaction that alongside postoperative adhesion bands, reduces bowel peristalsis, causes ileus, obstruction, distention, and increases pain⁽⁴⁾. Increased exposure of the intestines to atmosphere and upward packing of bowel loops for clearing the operative field during the surgery are other reasons mentioned in the literature⁽⁵⁾. Hence, keeping the peritoneal continuity in this surgery has been reported as an important milestone in reducing postoperative complications^(2,5,9-12).

To this end, 2 main techniques were introduced over the years. The first technique was by Kulkarni⁽²⁾ which indicated an extra-peritoneal approach with small infra-um-

bilical incision and retrograde cystectomy. In their long time follow up results of 180 patients published in 2018⁽¹³⁾, there was a considerable decrease in gastrointestinal complications, (5% vs. 15.8%, $p < 0.001$) and intestinal obstruction rate (1.7% vs. 7.8%, $p = 0.002$) in comparison with transperitoneal technique.

The other technique introduced by Roth et al⁽⁴⁾ in 2011 indicated a conventional transperitoneal approach with bilateral readaptation of the dorsolateral peritoneal layer with flaps that they created at the start of the surgery in order to omit the contact of intestines with the denuded surface of the pelvic wall and iliac vessels. Although with this style, the amount of time that the intestines are exposed to atmosphere is not decreased, they reported a significant decrease in pain and fewer bowel complications in the early postoperative days. This group performed a randomized trial based on this method⁽⁶⁾ and in their medial follow up of 59 months, the effects of readaptation was again resurfaced with less pain and better gastrointestinal function.

Concurrent with previous studies, our results indicated a considerable decrease in early postoperative gastrointestinal complications (Ileus , obstruction, anastomosis leak and urine leak) and wound infection. Moreover, the lower operation time in EP group meant faster surgery with limited time of bowel exposure to air which had an important role in reducing postoperative ileus⁽⁵⁾. In addition to decreased gastrointestinal problems, this technique is very advantageous in performing the most delicate part of the surgery, which is preserving the striated sphincter, at the beginning where the surgeon is the sharpest. This will allow for better urethral preservation

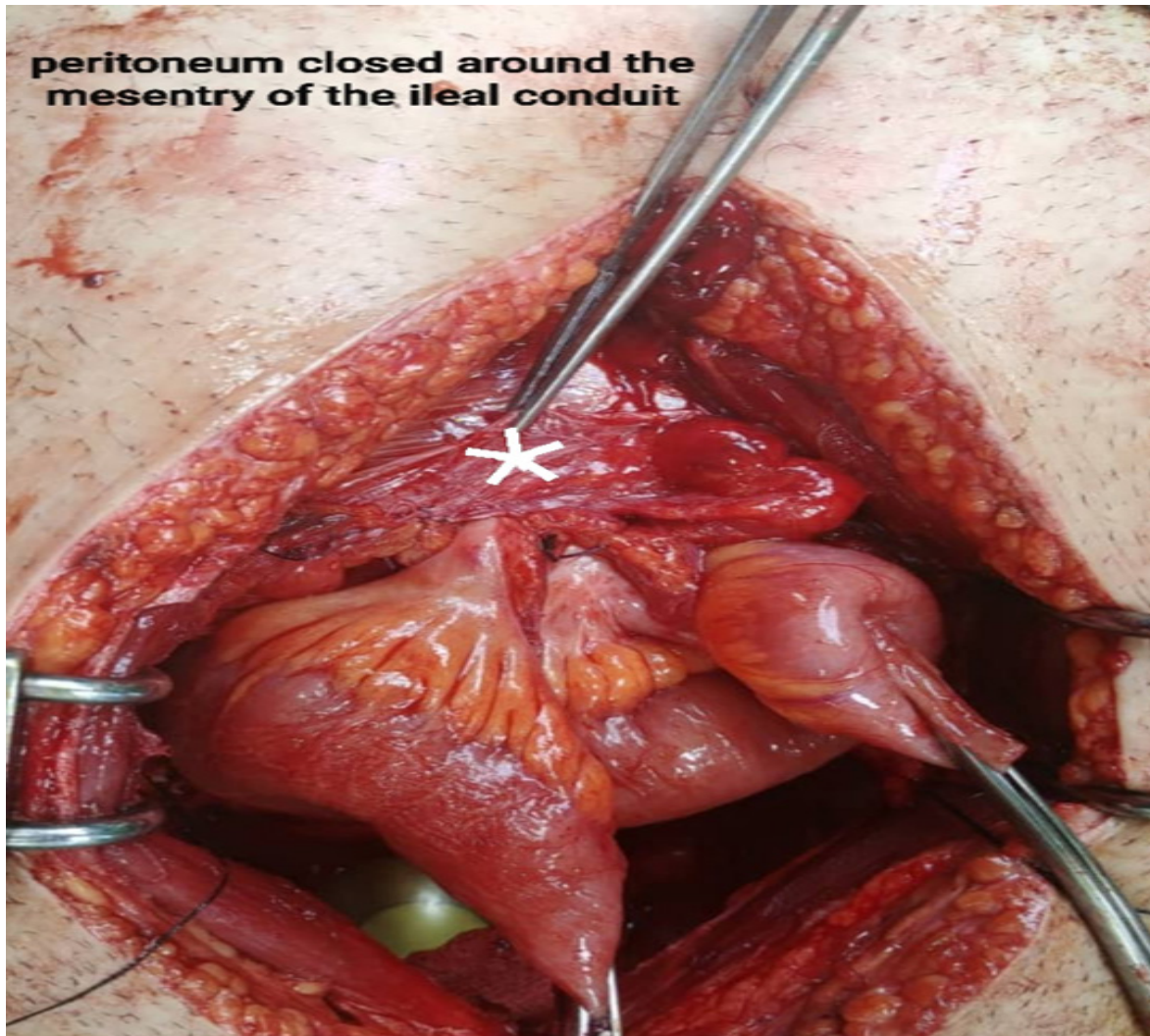


Figure 2. Readaptation of the peritoneal integrity by stitching the peritoneum to the mesenteric pedicle (*).

and sutures and better continence in orthotopic surgeries. Although in theory this idea seems reasonable but none of the studies so far could not demonstrate any difference between the 2 procedures in this regard^(3,5,12,13). This could be explained by the low number of orthotopic surgeries and no randomized trials, since difficult cases will mostly end up in conduit diversion.

Wound infection were lower in EP group (19% vs. 7%, $P = 0.02$). All were superficial infections which were resolved by bed side opening of stitches and irrigation. No dehiscence was encountered in the early post op period. Although for better quantifying the effect of small infra-umbilical incision in preventing dehiscence or hernia formation, longer follow-up would be needed. A concern with this technique is the increased chance of pelvic lymphocele formation. Because the peritoneum is closed, the lymph will no longer be absorbed and most probably create collections in the pelvic cavity, which concomitantly increase the chance of infection or deep vein thrombosis. In our series, we didn't have lymphocele formation. This could be due to our technique of meticulous ligation of all lymph vessels with silk tie stitches during the lymphadenectomy. However, in other reports which did have lymphocele formation,

the difference was either not significant^(4,13) or it did not cause any other major problems and all were resolved by less invasive measures⁽¹²⁾.

One of the major critics for extra-peritoneal procedure was its oncologic efficacy and the chance of residual tumor cells over peritoneum^(2,3,5,12-14). Considering that, some of the series only included cT1-T2 tumors and lesions away from the dome and posterior wall as their inclusion criteria^(2,3). In an interesting study by Zhu et al.⁽¹⁴⁾ the characteristics of patients suitable for extra-peritoneal approach were evaluated. They performed ex vivo biopsies of the peritoneum overlying the bladder in 136 cystectomy specimens (either random or from gross suspicious lesions). In their report, patients with T2-T4 stage, positive lymph nodes or non-urothelial histologies, were not good candidates for peritoneum preservation. Albeit, in two other studies which included >T2 patients and had mean follow up of 37⁽¹²⁾ and 70⁽¹³⁾ months, the rate of local recurrence and distant metastasis were similar, indicating that EP approach is applicable even in higher stages. The readaptation technique of Roth⁽⁴⁾ and Vartolomei⁽⁹⁾ also did not show any oncologic inferiority which was not surprising, since their procedure was essentially the

transperitoneal approach with an additional step of re-adaptation of peritoneum at the end of the surgery.

Given the lack of confirmed oncologic inferiority of EP technique for higher stages, we did include all clinical stages in this study. Although, due to short follow up, no comment can be made on the oncologic safety as it requires longer surveillance.

Missing intra abdominal metastases is another oncologic concern in EP approach. Nevertheless, the chance of its occurrence is very slim because of comprehensive pre-operative evaluation and in none of the series, including ours, no metastases was encountered during the surgery.

A few limitations of this study should be regarded. The patients' information were retrospectively collected which is susceptible to information bias in data insertion and collection. The number of included patients was limited and the follow up was short for deciding about longer term complications and oncologic efficacy and since this is not a randomized trial, bias in patient selection is pertinent to this study.

CONCLUSIONS

EPRC is a feasible option with tangible effects in reducing the post operative morbidity, especially the more prevalent gastrointestinal complications. Our technique while benefits from this approach by starting extra-peritoneally and releasing the urethra and sphincter meticulously at the beginning, it also permits the examination of the overlying peritoneum at the end of the cystectomy for its appearance and decision for its preservation or removal.

CONFLICT OF INTEREST

None declared by the authors.

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