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[Daniel Porav-Hodade](#) , [Silvestru-Alexandru Big](#) ^{*} , [Vlad-Ilie Barbos](#) , [Radu Galis](#) ^{*} , Bogdan Gherle ,
Ernő Jerzicska , Victor Ona , Bogdan-Ovidiu Feciche

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Article

Extraperitoneal Open Radical Cystectomy: A New Standard in Frail Patients with Muscle-Invasive Bladder Cancer?

Daniel Porav-Hodade ^{1,2}, Silvestru-Alexandru Big ^{3,*}, Vlad-Ilie Barbos ³, Radu Galis ^{4,5,6,*}, Bogdan Gherle ⁷, Ernő Jerzicska ⁸, Ona Victor ⁹ and Bogdan-Ovidiu Feciche ^{3,10}

¹ Department of Urology, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540139 Târgu Mureș, Romania

² Department of Urology, Clinical County Hospital Mures,, 540136 Târgu Mureș,, Romania

³ Department of Urology, Bihor Emergency Clinical County Hospital, 410169 Oradea, Romania;

⁴ Department of Neonatology, Emergency County Hospital Bihor, 50 Clujului Street, 410053 Oradea, Romania.

⁵ Department of Neonatology, Poznan University of Medical Sciences, 10 Fredry Street, 61-701 Poznan, Poland

⁶ Department of Medical Sciences, University of Oradea, 1 University Street, 410087 Oradea, Romania. (R.G.)

⁷ Doctoral School of Biological and Biomedical Sciences, University of Oradea, 1 University Street, 410081 Oradea, Romania

⁸ Department of Cardiovascular Surgery, Bihor Emergency Clinical County Hospital, 410169 Oradea, Romania;

⁹ Department of Urology, Clinical Municipal Hospital, 400139 Cluj-Napoca, Romania

¹⁰ Department of Urology, Faculty of Medicine and Pharmacy, University of Oradea, 1 University Street, 410087 Oradea, Romania

* Correspondence: alex_big_jsd@yahoo.ro (S.-A.B.); raduoradea@yahoo.co.uk (R.G.); Tel.: +40-758501429 (S.-A.B.)

Abstract: Background/Objectives: Radical cystectomy (RC) represents one of the most complex and morbid surgical procedures in Urology. Extraperitoneal open RC has emerged as an alternative to traditional transperitoneal approach for the treatment of muscle-invasive bladder cancer. Frailty is one of the most important risk factors for perioperative morbidity and mortality and this category of patients can benefit the most with the extraperitoneal approach. The purpose of this study was to evaluate the feasibility and the safety of extraperitoneal open RC in our experience; **Methods:** We retrospectively collected the data of 75 frail patients who underwent extraperitoneal open RC, performed by a single experienced surgeon. We assessed the frailty status using the simplified frailty index (sFI). We recorded data regarding general characteristics, intraoperative, pathological, postoperative complications and mortality (within 90 days); **Results:** We analyzed 61 men and 14 females with sFI equal or higher than 3. The median age was 77 years. Fifty-one patients had ASA score of 3 or more. Sixty procedures were with radical intention, while fifteen were palliative. Cutaneous ureterostomy was performed in 70 cases and extraperitonized ileal conduit in five cases. The median operative time was 150 minutes. The median blood loss was 400 mL. The median time up to flatus was 2 days. The median postoperative stay was 7 days. Thirteen patients had Clavien-Dindo 3 or 4 complications. Two patients died in first 90 days postoperatively; **Conclusions:** The extraperitoneal open RC in frail patients demonstrated to be a feasible and safe alternative approach in definitive or palliative setting in our experience.

Keywords: bladder cancer; extraperitoneal open radical cystectomy; reperitonization; frailty

1. Introduction

Bladder cancer (BCa) is one of the most common urological malignancies worldwide [1], being the 9th most common cancer worldwide [2]. In BCa, approximately three-quarters of the cases are found in men [3]. In the past decade, the incidence of BCa in Europe has increased, while mortality

has decreased. In Asia, however, the opposite has occurred, with a decrease in incidence but an increase in mortality due to BCa in men [4]. Unfortunately, 5-year survival rate for BCa has remained relatively low compared to other urological cancers [5]. Around 75% of BCa patients present with disease limited to the mucosa (stage Ta, CIS) or submucosa (stage T1) [6]. The remaining patients, unfortunately, present with MIBC or metastases at the time of their initial evaluation.

According to the international guidelines, radical cystectomy (RC) is the recommended treatment for localized muscle-invasive bladder cancer (MIBC), very high-risk NMIBC (non-muscle-invasive bladder cancer), and BCG (Bacillus Calmette-Guérin)-unresponsive NMIBC [7–9].

The transperitoneal approach is the standard method for RC, although the gastro-intestinal, wound-related and infectious complications contribute to the still increased morbidity of procedure [10].

Extraperitoneal RC was proposed with the aim of reducing the morbidity of procedure. The peritoneum is not entered in the initial steps of procedure, but only the serosa covering the bladder dome is excised in the end followed by reperitonization. This approach presents several potential advantages compared to the traditional transperitoneal route, including reduced surgical trauma to the abdominal cavity, fewer postoperative complications, and potentially quicker recovery times. Extraperitoneal approach helps minimize the risk of ileus, peritonitis, and adhesions, which are especially worrisome in frail patients. [10,11].

Although initial concern regarding radicalness of surgery with the extraperitoneal approach, there are comparative studies demonstrating the two approaches have similar oncological outcomes [12].

More than chronological age, frailty is a distinct entity and refers to an increased vulnerability to stressors due to the cumulative effects of various conditions over time, independent of the normal aging process. It is one of the most important predictors of perioperative morbidity and mortality in RC [13].

The aim of this study was to evaluate the perioperative results and complications of open extraperitoneal radical cystectomy.

2. Materials and Methods

2.1. Study Population

We retrospectively included 75 patients considered frail who underwent open radical cystectomy by extraperitoneal approach, between March 2014 and March 2024. The assessment of the frailty was made by calculating the simplified frailty index, as described by Sathianathan et al [14]

Sixty procedures were elective, with curative intent, for nonmetastatic MIBC, while in 15 cases it was performed in palliative setting (e.g. bladder tumour with refractory hematuria). In all cases, the surgical intervention was performed by the same surgeon, with high experience in open uro-oncological surgery.

The clinical staging was established based on preoperative Computed Tomography chest, abdomen and pelvis.

We recorded the patients' characteristics in our database during the hospital stay for perioperative data: gender, age, body mass index (BMI), clinical TNM stage, preoperative laboratory test results, ASA and frailty scores, intraoperative data (total operative time, estimated blood loss, number of patients who required blood transfusion, type of urinary diversion, type of anesthesia), intraoperative incidents, immediate postoperative complications, postoperative laboratory tests, time up to the first flatus (Recovery of Bowel Function), postoperative hospital stay.

The postoperative complications occurring after discharge (within 90 days after surgery), were assessed during follow-up visits. The postoperative complications were graded according to the Clavien-Dindo classification [15].

All patients offered their informed consent for participation in our study.

2.2. Surgical Technique

Preoperative anesthetic risk was assessed using ASA (American Society of Anesthesiologist) score. Forty-six patients underwent general anesthesia (with orotracheal intubation), while 29 patients underwent epidural anesthesia.

Subjects with negative urine culture received prophylactic antibiotics one hour before skin incision, while those with preoperative positive urine culture received at least 3-5 days of antibiotics preoperatively according to antibiogram. Mechanical and pharmacological antithrombotic prophylaxis was perioperatively applied in all cases. Bowel preparation before surgery was not applied at all, except the five cases where ileal conduit was performed.

We placed the patient in Trendelenburg position (15-degrees) with the surgical slightly flexed just above iliac crest. The Retzius space is entered using a median infra-umbilical incision. The pelvic parietal peritoneum was bluntly pushed cephalad up to the level of common iliac vessel. The vas deferens were dissected and sectioned to allow a better medial mobilization of peritoneum. The avascular lateral perivesical space on each side is bluntly developed up to the endopelvic fascia, as well as the retrocolic space. We isolated on vascular loops the ureters where they cross the iliac vessels and proceeded with their dissection as caudally as possible. The superior vesical artery was identified, clipped or ligated, then sectioned. We isolated, ligated and sectioned the retroureteral bladder pedicles, that allow an extensive posterolateral mobilization of the bladder. The endopelvic fascia was incised on both sides, then the lateral prostatic pedicles were isolated, ligated and sectioned. Then, we proceeded with the dissection of prostate apex. We sectioned the puboprostatic ligaments, we ligated and sectioned the dorsal vascular complex Santorini and the urethra.

The posterior side of the prostate is dissected off the Denonvillier fascia, then entire specimen can be detached off the inferior peritoneum. Only that portion of peritoneum that covers the posterior bladder surface is excised en-bloc with the specimen.

Except emergency procedures performed with hemostatic purpose only, we proceeded with standard lymph node dissection (LND) after completion of radical cystectomy.

The ureterostomy were performed, then the continuity of peritoneum was reestablished using absorbable suture before the abdominal wall to be closed.

In cases where ileal conduit was performed, the peritoneum was closed around the mesentery of the conduit.

2.3. Statistical Analysis

The median and range for continuous variables (as they are not normally distributed according to the Shapiro-Wilk test) and frequencies and percentages for categorical variables were used. For the statistical studies, IBM SPSS 19 and Microsoft Excel 2019 were utilized.

3. Results

The general characteristics of patients are presented in Table 1. A total of 75 patients, 61 males and 14 females, that met the frailty criteria (sFI equal or higher than 3) were analyzed. The median age was 77 years (range: 59-84 years).

Table 1. The general characteristics of patients.

Variable	Value
Age at surgery [years], median (range)	77 (59-84)
Males, n (%)	61 (81.3)
Females, n (%)	14 (18,7)
BMI [kg/m²], median (range)	26 (17-35)
Obstructive renal failure, n (%)	20 (26.7)
Moderate-severe anemia, n (%)	35 (46.7)
Hypoalbuminemia, n (%)	33 (44.0)
ASA score	
ASA 2, n (%)	24

ASA 3, n (%)	47
ASA 4 n (%)	4

BMI = Body Mass Index; ASA = American Society of Anaesthesiologists.

Twenty patients had a degree of obstructive renal failure (serum creatinine over 2 mg/dL and hydronephrosis). Thirty-five patients had preoperative moderate or severe anemia (Hb<10 g/dL) and thirty-three had hypoalbuminemia. The median BMI was 26 kg/m2 (range: 17-35 kg/m2).

Regarding preoperative anesthesia risk, 24 patients had ASA score 2 and 51 had ASA score 3 or higher, respectively.

The surgical procedure had radical intention in 60 cases and palliative purpose (e.g. for refractory hematuria) in 15 cases, when standard lymph node dissection was not performed. We performed bilateral direct ureterostomy in 65 cases, while extraperitonized ileal conduit was used as urinary diversion in ten cases. Forty-six patients underwent only regional anesthesia (peridural or combined spinal / peridural anesthesia) and 29 patients general anesthesia, respectively.

The intraoperative and postoperative results are shown in Table 2. The median operative time was 150 minutes (range: 90-210 minutes). The median blood loss was 400 mL (range: 200-1500 mL). Thirty percents of patients needed blood transfusions. The median time up to flatus (postoperative ileus) was 2 days (range: 1-7 days). The median postoperative hospital stay was 7 days (5-14 days). Thirteen patients had Clavien-Dindo 3 or 4 complications. Two of them required surgical reintervention where intestinal lesions related to the reperitonization were identified and solved. Lymphocele was encountered in 6 cases, five of them drained percutaneously and one fenestrated laparoscopically. Nine cases were complicated by superficial (suprafascial) wound dehiscence, treated with daily wet-to-dry dressings, antibiotics, and eventually secondary suture in three cases.

Table 2. Intraoperative and postoperative results.

Variable	Value
Median operative time [minutes], median (range)	150 (90-210)
Median blood loss [mL], median (range)	400 (200-1500)
Median time to flatus [days], median (range)	2 (1-7)
Blood transfusion, n (%)	23 (30)
Urinary diversion	
Cutaneous ureterostomy, n (%)	65 (86.7)
Ileal conduit, n (%)	10 (13.3)
Intraoperative incidents	
Rectal injury, n (%)	1 (1.3)
External iliac vein injury, n (%)	1 (1.3)
Obturator nerve injury, n (%)	1 (1.3)
Postoperative complication	
Clavien III, n (%)	11 (14.7)
Clavien IV, n (%)	2 (2.7)
Clavien V, n (%)	2 (2.7)
Duration of postoperative hospital stay [days], median (range)	7 (5-14)

Four patients had ileus (postoperative nausea / vomiting and abdominal distension, necessitating nasogastric tube insertion, discontinuation of oral intake and / or parenteral nutrition). Postoperative venous thromboembolism was encountered in two cases, while one patient presented acute coronary syndrome.

Rectal injury was encountered in one case, intraoperatively recognized and repaired by primary suture.

Two patients died in first 30 days postoperatively, but without any intraoperative death. The pathological results were summarized in the Table 3.

Table 3. The general characteristics of patients.

Variable	Value
Pathological T stage	
pT2, n (%)	48 (64)
pT3, n (%)	23 (30,7)
pT4, n (%)	4 (5,3)
Pathological N stage	
Lymph node dissection, n (%)	60 (80)
pN0, n (%)	45 (60)
pN1, n (%)	12 (18)
pN2, n (%)	3 (4,4)
Concomitant prostate adenocarcinoma	15 (20.0)
Positive surgical margins, n (%)	1 (1.3)

4. Discussion

The ageing of the population is making the management of MIBC in older individuals a challenging issue. Bladder cancer (BCa) is more likely to affect this category of patients, as the age-specific incidence rates gradually increase after 50 years-old [16].

RC is the gold standard treatment of the MIBC, alternatives like transurethral resection alone or trimodality treatment [17] having similar oncological outcomes in selected cases only [7].

The complication rates after the standard transperitoneal RC remains high, especially in morbid patients. In a study on the early morbidity of radical cystectomy, Shabsigh et al. reported a Clavien III–V complication rate of 13%. Among these, the most frequent complications were gastrointestinal (29%), infectious (25%), and wound-related (15%) [18].

Even though conventional transperitoneal radical cystectomy is the standard approach for muscle-invasive bladder cancer [19], the procedure is associated with significant morbidities such as urinary leakage, ileus, and infections [20]. The cause is supposed to be the deperitonized pelvic wall that comes in contact with the bowel serosa, combined with the increased exposure of the bowels to the atmosphere, resulting in an increased local inflammatory reaction and, in consequence, reducing bowel peristalsis, increased ileus duration, obstruction, distention, and increases pain [20,21].

An extraperitoneal retrograde approach for RC and pelvic LND was published for the first time in 1999 by Kulkarni et al. [22] to reestablish the natural compartmentalization between the gastrointestinal and the urinary tract and to minimize the handling and prolonged exposure of the intestines to the air. Although there are several differences between our technique and the original one, the main principle regarding peritoneal continuity was preserved. Only peritoneum of the bladder dome surface was excised en-bloc with the specimen at the final of exeresis, then the remaining serosa was completely closed (if the cutaneous ureterostomy is performed) or closed around the mesentery of the conduit. The extraperitoneal RC was adopted by many surgeons, with various modifications [6].

In the retrospective study of the Kulkarni et al. published in 2018, they compared the extraperitoneal approach with the transperitoneal one in open RC. They found a statistically significant lower rate of ileus (5% vs. 15.8%, $p < 0.001$) and delayed intestinal obstruction rate (1.7% vs. 7.8%, $p = 0.002$) in the first group. The rates of other early and delayed complications were slightly lower after extraperitoneal RC, but the results were not statistically significant [20].

Another study published by Özkaptan et al. in 2020 [23] that compared the perioperative outcomes of the extraperitoneal antegrade and transperitoneal open RC with ileal conduit performed in their center. They found statistically significant superior results regarding the postoperative hospital stays (median: 9 versus 10 days, $p=0.042$), the bowel function recovery (median: 3 versus 4 days, $p<0.01$) and the rate of postoperative ileus (5.8 versus 19.2%, $p=0.043$) in the first group.

A systematic review and meta-analysis compared the perioperative outcomes after transperitoneal versus extraperitoneal RC in the treatment of BC, including 1207 patients (619 in the first group and 588 in the other one) was published in 2023 by Leonardo et al. [19]. The patients

undergoing extraperitoneal RC had significantly lower occurrence of postoperative ileus, but the results regarding rate of the Clavien III-V complication, estimated blood loss, operative time, postoperative hospital stay duration and infections were not conclusive, without statistically significant differences between groups.

The urinary diversion chosen for the most patients was cutaneous ureterostomy, that can partially explain the lower rates of gastrointestinal complications encountered in our study group when compared with the literature data regarding this type of approach [24,25].

The role of readaptation of posterolateral peritoneum after RC with LND was evaluated in a prospective randomized trial that included 200 patients. The patients undergoing this technique had less postoperative pain, earlier recovery of bowel function and fewer complications in the first 30 days postoperatively [26].

The management of MIBC in older and frail patients remains a controversial topic in literature. Subjects with BCa had at the time of diagnosis the highest median age among all cancer types and more chronic comorbidities when compared with the general population (eight versus four comorbidities) [27]. Frailty is an independent entity characterized by an accelerated decline in physical and cognitive resilience to the stressors like infections or surgery. It is a strong predictor for perioperative complications, impaired quality of life and mortality [13].

Radical cystectomy (RC) carries a significant perioperative mortality rate [18], ranging from 0.8% to 3% [28,29]. However, this mortality rate is inversely related to the experience of the surgical centers, with lower mortality observed in high-volume academic institutions [30].

Given the increased morbidity of procedure, RC is not widely accepted as a standard treatment for MIBC in these categories of patients. Thus, it is usually considered when the other alternatives are not feasible or have failed. If the perioperative risk is acceptable, many patients with BC are willing to undergo radical surgery. There is not an objective stratification of the perioperative risk for major surgery, which contributes to the reluctance of urologists to offer RC in this category of patients [27].

We used the sFI to measure the frailty. It has five items, 1 point attributed for each of them: functional status, DM (diabetes mellitus), COPD (chronic obstructive pulmonary disease), CCF (congestive cardiac failure), and hypertension that requires treatment. Patients with sFI more or equal than 3 have higher rates of Clavien III-V complications and early postoperative mortality. There are studies that demonstrate the superiority and the simplicity of this score in predicting the postoperative complications following RC when compared with traditional methods like ASA score. The score helps us not necessarily contraindicate the radical surgery, but to select the category of patients which could potentially benefit the most from less morbid approaches and from health-optimizing interventions after surgery [14,31].

Despite initial concerns about the radical nature of surgery using the extraperitoneal approach, comparative studies have shown no statistically significant differences in oncological outcomes between extraperitoneal and transperitoneal radical cystectomy (RC) [12]. The pathological results in our series are comparable with those found in literature.

The main drawbacks of this study are represented by the retrospective nature of data collection, the relatively low patient number and the lack of a control group to compare the outcomes.

Although we are in the era of robotic-assisted surgery, we consider that extraperitoneal open approach can still find the place for frail patients that cannot tolerate general anesthesia, hypercapnia and/or steep Trendelenburg position.

5. Conclusions

The extraperitoneal open RC in frail patients demonstrated to be a feasible and safe alternative in definitive or palliative setting in our experience, with acceptable outcomes. Further prospective, comparative, multicentric studies are needed to generalize the conclusion.

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B.O.F., S.A.B.; writing—review and editing, R.G., S.A.B., B.O.F.; visualization, V.I.B., E.J., O.V.; supervision, D.H.P.; project administration, D.H.P., B.O.F.; All authors have read and agreed to the published version of the manuscript

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to restrictions.

Conflicts of Interest: The authors declare no conflicts of interest.

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