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ORIGINAL PAPER

Extraperitoneal cystectomy with ureterocutaneostomy derivation in fragile patients - should it be performed more often?

Rafaela Malinaric [1], Guglielmo Mantica [1], Federica Balzarini [1], Carlo Terrone [1], Massimo Maffezzini [2]

[1] Department of Urology, San Martino Hospital, University of Genoa, Genoa, Italy;
[2] Department of Urology, Hospitals of Legnano and Magenta, Milan, Italy.

Summary *Introduction and objectives: Radical cystectomy (RC) continues to be standard of care for muscle-invasive bladder cancer and recurrent or refractory non-muscle invasive bladder cancer. Unfortunately, it has high rates of perioperative morbidity and mortality. One of the most important predictors of postoperative outcomes is frailty, while the majority of complications are diversion related. The aim of our study was to evaluate safety of extraperitoneal cystectomy with ureterocutaneostomy in patients considered as frail.*
Materials and methods: We retrospectively collected data of frail patients who underwent extraperitoneal cystectomy with ureterocutaneostomy from October 2018 to August 2020 in a single center. We evaluated frailty by assessing patients' age, body mass index (BMI), nutritional status by Malnutrition Universal Screening Tool, overall health by RAI (Risk Analysis Index) and ASA (American Society of Anaesthesiologists) score, and laboratory analyses. We observed intraoperative outcomes and rates of perioperative (within 30 days) and early postoperative (within 90 days) complications (Clavien-Dindo classification). We defined extraperitoneal cystectomy with ureterocutaneostomy as safe if patients did not develop Clavien Dindo IIIb, or worse, complication.
Results: A total of 34 patients, 3 female and 31 male, were analyzed. The median age was 77, BMI 26, RAI 28, ASA 3 and the majority had preexisting renal insufficiency. Blood analyses revealed presence of severe preoperative hypoalbuminemia and anemia in half of our cohort. Intraoperative median blood loss was 250 cc, whilst operative time 245 min. During perioperative period 60% of our cohort developed Clavien Dindo II complication and during early postoperative period 32% of patients required readmission. One death occurred during early postoperative period (2.9%). After 12 months of follow-up, we observed stability of the renal function for most patients.
Conclusions: We believe that extraperitoneal cystectomy with ureterocutaneostomy could be considered as a treatment option for elderly and/or frail patients.

KEY WORDS: *Bladder cancer; Extraperitoneal cystectomy; Ureterocutaneostomy; Frailty; Feasibility.*

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INTRODUCTION

When both sexes are considered, bladder cancer is one of the most common cancers worldwide, sitting at the 7th place (1). Although the majority of patients present with non-muscle invasive disease, bladder cancer can often recur or even progress (2).
Currently, *radical cystectomy* (RC) is considered as the gold standard for treating muscle-invasive bladder cancer (1). Unfortunately, it continues to be one of the surgical procedures with the highest rates of morbidity and mortality to date (3).
Although chronological age is an important risk factor for development of intra- and peri-operative complications, several concurrent losses in resources, should be considered in the estimation of surgical risk (4).
Actually, frailty has been recognized as the most important predictor of poor postoperative outcomes. Although there is still no consensus on clinical definition of frailty (6), some authors refer to it as "*a state of reduced physiologic reserve beyond that would be expected with normal aging*". It is thought to be the final product from the cumulative effect of multiple physiologic changes over time (5).
Fried et al. designed a list that could help clinicians in assessing general physical state of patients and listed these components as a part of frail phenotype: a) self-reported weight loss; b) self-reported exhaustion; c) low energy expenditure; d) slow gait speed; e) weak grip strength (6). Frail patients have a compromised pulmonary function, decreased time to desaturation, higher hypoxia and hypercarbia. Altered renal and hepatic functions are also frequent, with consequent decreased drug metabolism, dehydration, electrolyte disbalance and increased haemorrhagic and drug toxicity risk. Lastly, because of the sarcopenia and generally reduced serum albumin, they are more prone to hypothermia and are more sensitive to effect of the anaesthetics (7). Consequently, a frail patient is more vulnerable to a stressor event and has a lower capacity of recovery after the stressor stimulation ceases. Furthermore, the prevalence of frailty increases with age. Considering that the life expectancy has increased by more than two years per decade since the 1960s (8), the proportion of elderly population diagnosed with bladder cancer undergoing cystectomy has been rising as well.
Although not conducted on a frail population, *Berger et al.* published a retrospective, multicenter study comparing the rates of complications in *ureterocutaneostomy* (UCS) and urinary diversion using bowel. They observed reduced operative time, shorter stay in intensive care unit

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and significantly lower complication rates (graded as Clavien III-V) in UCS group (9).
Moreover, a great part of data present in the literature reports that most perioperative and postoperative complications are diversion realted (10).
When treating frail patients, the main goal is, when possible, to achieve radicality, or, when this is not achievable, to provide a patient a decent quality of life. In fact, by performing cystectomy, patients will not experience anymore recurrent hematuria, suprapubic pain, lumbar discomfort, dysuria or urinary retention.
A lot of studies demonstrated successful outcomes after surgery performed on frail patients, but there is little evidence on patients undergoing radical cystectomy (11-13).
Therefore, the aim of our study was to evaluate the safety of extraperitoneal cystectomy with UCS performed on frail and/or elderly patients.

Materials and methods

Study design

We retrospectively collected clinical and pathological data of frail patients who underwent extraperitoneal cystectomy with UCS from October 2018 to August 2020 in a single center.
Patients were considered frail if they met 3 or more of the following criteria: advanced age (> 70), low or high *body mass index* (BMI) (< 18 and > 25), altered nutritional status [*Malnutrition Universal Screening Tool* (MUST) > 1] (14) and altered general physical health [*Risk Analysis Index* (RAI) > 25] (15), *American Society of Anesthesiology* (ASA) score > 3 (16), preoperative anemia (< 12 g/dL), renal insufficiency [serum creatinine (Crs) > 1.3 g/dL, eGFR < 60] and hypoalbuminemia (< 3 mg/dL).
The MUST questionnaire considers three factors: BMI, unintentional weight loss and inability of the oral nutritional intake due to acute illness (> 5 days). After appropriate evaluation, risk of malnutrition can be appropriately designated as low risk (score 0), medium risk (score 1), high risk (score 2 or more) (14).
Risk Analysis Index is a simplified Porock's 6-months mortality Index developed in 2015. It assesses age, sex, presence of malignancy, medical comorbidities, residence, cognition and daily activities. Once the questionnaire is filled, the score matches the risk of perioperative and postoperative complications development (15). Lastly, patients were assigned their ASA score (16).
Evaluating patients in this, more holistic manner, we were able to identify the most fragile, sarcopenic, malnourished patients with highly catabolic disease that could benefit from extraperitoneal cystectomy with UCS.
Preoperatively all patients underwent CT or MRI imaging in order to complete clinical staging.
Consent form was obtained from all the patients prior to surgery.
All patients were operated by one, same surgeon (M.M.) with more than 200 extraperitoneal cystectomies performed and 2 decades of experience in the field of open, uro-oncologic surgery.
Female patients who were considered frail and with advanced disease underwent genital sparing extraperitoneal cystectomy, whilst frail male patients underwent standard extraperitoneal cystectomy. Lymph node dissection was performed only in significant, clinically evident lymphadenopathy (gross and palpable lymph nodes).
Frail patients with non-metastatic disease underwent radical extraperitoneal cystectomy with standard lymph node dissection (up to the common iliac arteries).
All patients received UCS as urinary diversion, and all the procedures were performed using the open approach. Intraoperatively 4.8 Ch "*Bracci pattern*" ureteral catheters were positioned. Two weeks postoperatively "*Bracci*" catheters were substituted with ureteral catheters in polyurethane (*Wiruthan*).
ERAS protocol was implemented, when possible, with epidural catheter positioning, antithrombotic prophylaxis with heparin 100 units/kg/24h (fractioned in two doses) for 3-4 weeks, antibiotic prophylaxis with *Clindamycin* 1200 mg/24h and *Metronidazole* 1000 mg/24h (both fractioned in two doses) for 48 hours postoperatively. In case of allergies, they were substituted by *Piperacillin/Tazobactam* 13.5 g/24h (fractioned in three doses). All drugs were adjusted based on cardiac, renal and hepatic function.
Postoperatively patients entered our standard follow-up protocol, with CT scans repeated quarterly or biannually, complete blood panel, urinalysis and urine cytology, depending on the intent of cystectomy (curative or not) and their final pathology findings. Ureteral catheters were substituted in ambulatory setting every 3-4 weeks in absence of infections, calcifications and obstruction.

Data collection and classification of complications

Patients' information was collected from hospital database.
We assessed duration of the surgery, anaesthesia protocol and blood loss, whilst data regarding histopathological reports were recorded according the TNM classification approved by the *Union International Contre le Cancer* (UICC) (8th Edn.) (17).
Subsequently, we observed duration of the hospital stay, hematologic and biochemical alterations, perioperative (within 30 days) and early postoperative (within 90 day) complications (*Clavien Dindo* classification) (18) and readmission rates.

Outcomes

We hypothesized that this surgical technique would be a safer approach when treating frail and elderly patients, decreasing the risk of perioperative morbidity and mortality. We considered extraperitoneal cystectomy with UCS a safe procedure if patients did not develop any Clavien Dindo > IIIb complication.

Statistical analysis

Descriptive statistics included frequencies and proportions for categorical variables.
Means, medians, and *interquartile ranges* (IQR) were reported for continuously coded variables.
We considered age, BMI, MUST score, ASA score, RAI score, preoperative and postoperative laboratory results, tumor pathological stage and postoperative outcomes. The Mann-Whitney and Fisher's exact test examined the

statistical significance of mean and distribution differences among patients with or without complications.
The characteristics of patients with and without complications were compared with the Mann-Whitney and Fisher's exact tests, accordingly. All tests were two sided with a level of significance set at $p < 0.05$.
R software environment for statistical computing and graphics (version 4.1.3) was used for all analyses (*R Core Team 2021*). R: A language and environment for statistical computing. *R Foundation for Statistical Computing, Vienna, Austria*.
Available at: *URL https://www.R-project.org/.*)

Results

Patient population and perioperative characteristics

We collected data of 34 patients, 3 (8.8%) females and 31 (91.2%) males, that met the frailty criteria. The median follow-up was 12 (5.75-15.25) months.
The majority of the patients (86%) were 70 years old or older, with median age of 77.5 (IQR 71.1-80.2), and were smokers (58.8%). Median BMI was 26 and most of them already had preexisting renal insufficiency (median Crs 1.33 mg/dL (IQR 1.17-1.62), with an eGFR 35.5).
Seventeen (50%) patients reported unvoluntary weight loss three months prior to surgery, 12 (35%) were medium risk for malnutrition, while 5 (15%) were high risk. All the high-risk patients were referred to the specialized dietitian (Table 1).
Median RAI score was 28 (IQR 25.0-31.0), in fact 30 (88%) patients scored over 25. Furthermore, most patients (23, 68%) were classified as ASA 3 (Tables 1-2).
Thirty-three (97%) patients had a preoperative hypoalbuminemia (serum albumin ≤ 3 g/dL) and 22 (64.7%) anemia (hemoglobin ≤ 12.5 g/dL) (Table 2).

Table 1.
Descriptive characteristics of 34 patients treated with extraperitoneal cystectomy and ureterocutaneostomy from October 2018 to August 2020

Characteristics	N = 34 *
Age, (years)	77.5 (71.1, 80.2)
Female	3 (8.8%)
Male	31 (91.2%)
BMI, (kg/m^2)	26.0 (24.0, 30.0)
Preoperative creatinine, (mg/dL)	1.33 (1.17, 1.60)
Preoperative albumin, (g/dL)	3.20 (2.62, 3.77)
Preoperative hemoglobin (g/dL)	12.15 (10.7, 13.28)
MUST score	
0	17 (50%)
1	12 (35%)
2	5 (15%)
ASA score	
1	1 (2.9%)
2	9 (26%)
3	23 (68%)
4	1 (2.9%)
RAI	28.0 (25.0, 31.0)

* *Median (IQR); n (%).*

Overall, 27 (79.4 %) patients presented with symptomatic disease including suprapubic pain, recurrent macrohematuria and urinary retention (Table 2).
Seven patients (20.5%) presented with BCG refractory disease. None of the patients underwent neoadjuvant chemotherapy because of late stage of the disease, or because of the general health status and advanced age. One patient did, however, undergo pelvic radiotherapy that caused actinic hematuria and severe anemization (Table 2).
Cystectomy was radical in 23 patients (68%) and palliative in 11 (34%) with no lymphadenectomy (Table 1).
Median duration of surgery (skin-to-skin) was 245 (124-420) minutes and registered blood loss was 250 (100-800) mL.
ERAS protocol was applied in all eligible patients (20 patients, 59%). On the contrary, 14 patients underwent general anesthesia with use of opioids for analgesia.
On the final histopathological examination 4 (12%) patients had a pTa urothelial tumor, 5 (14%) pT1, 9 (27%) pT2, 7 (20%) pT3 and 9 (27%) pT4, respectively. A mean of 8 lymph nodes per patients was removed and 4 patients (12%) had lymph node metastases. The same number of patients (4, 12%) had a distant organ metastasis *ab initio*.
Furthermore, in our cohort for 11 (32%) patients the surgery was not radical, and they did not undergo pelvic lymph node dissection. Finally, 5 (15%) patients had a positive surgical margin, all with pT4 tumor.

Clinical outcome

Median hospital stay was 13 (range 7-87) days.
Postoperatively, renal function remained stable (median creatinine increase was 0.09 mg/dL) for the majority of patients. Two patients had a major drop [from 6.2 mg/dL to 5.0 mg/dL on 3rd *postoperative day* (POD) and from 6.0 mg/dL to 4.4 mg/dL on 3rd POD], one had a major increase (from 3.8 mg/dL to 7.2 mg/dL 3rd POD).
Noticeably, the same patient who had an increase in Crs,

Table 2.
General patients' characteristics and number/percentage of patients divided by various subgroups.

Characteristics	N = 34 *
Age ≥ 75 years	33 (97%)
History of smoking	20 (58.8%)
BMI ≤ 21 or ≥ 25 (kg/m^2)	24 (70.6)
Preoperative albumin < 3 g/dL	33 (97%)
Preoperative hemoglobin < 12.5 g/dL)	22 (64.7%)
ASA score ≥ 3	25 (73.5%)
RAI score ≥ 25	30 (88.2%)
BCG refractory disease	7 (20.5%)
Pathological Stage > cT3	16 (47%)
cN+	8 (23.5%)
cM+	4 (11.7%)
Clinical symptoms	27 (79.4%)
More than one variable combined	34 (100%)

* *n (%).*

had a pT4 bladder cancer at the final pathology and a severe preoperative and postoperative hypoalbuminemia. Subsequently, he developed *surgical site infection* (SSI) during hospital stay and later required readmission.
Most patients passed gas in the 2nd POD (21 pts, 62%, range 1-3 POD) and one third of patients passed feces in 5th POD (10, 30%, range 3-15 POD).

Perioperative complications
During hospital stay 20 (58.8%) patients developed Clavien Dindo >/= II grade complication [12 SSI, 2 paralytic ileus, 1 acute kidney injury, 15 blood transfusions, 4 *urinary tract infections* (UTIs), 2 atrial fibrillations and 1 lymphocele]. Eight (24%) patients developed more than one complication requiring simultaneous administration of antibiotics and blood components.
Only 2 (5.9%) patients developed Clavien Dindo III complication (two deep subfascial infections, of which one with simultaneous evisceration). Both patients were treated with *Vacuum Assisted Closure Therapy* (VAC) (19), and the patient with evisceration underwent surgical correction using Linberg flap technique.
A strong association between perioperative hypoalbuminemia and SSI was noted. All the patients with SSI (12, 35.29%) had a marked hypoalbuminemia (≤ 3 g/dL) on the 3rd POD and the majority of them (10 patients) had it also preoperatively, being at medium/high risk of malnutrition.
An association between BMI (> 25) and septicemia was observed in 6 patients of 8 (75%) who developed fever.
Higher rates of complications and readmission rates were noted in patients that had ASA score > 3 and presented medium/high risk of malnutrition.
During perioperative period there were no deaths observed due to the surgical complications.

Postoperative complications
During early postoperative period (within 90 days) 11 (32%) patients required a readmission. Most of complications were infectious, refractory to the antibiotic therapy administered by general medicine physician: 2 SSIs (5.9%) and 5 UTIs (14.7%). Less frequent complications were: 2 lymphoceles (5.9%), 1 pulmonary thromboembolism (2.9%) and 1 intestinal subocclusion (2.9%).
All were classified as Clavien Dindo grade II (Table 3). Rates of readmission showed a similar trend.
Patients with complications had a significantly higher RAI score if compared with patients without complications (p = 0.027) (Table 4).
Lastly, one death occurred during early postoperative period (2.9%) due to recurrent UTIs and sepsis (Table 3).
At median postoperative follow-up of 12 (5.75-15.25) months, 7 (20%) patients were dead, 4 due to the disease progression and 3 due to non-cancer specific causes. Sixteen (47%) patients were alive without evidence of the disease recurrence.

Table 3.
Clavien-Dindo grading in relation to perioperative and early postoperative period.

	N = 34 *	N = 34 *
Complication (Clavien-Dindo)	**Perioperative (within 30 days)**	**Early postoperative (within 90 days)**
I	0 (0%)	0 (0%)
II	20 (58.8%)	11 (32.4%)
IIIa	1 (2.9%)	0 (0%)
IIIb	1 (2.9%)	0 (0%)
IV	0 (0%)	0 (0%)
V	0 (0%)	1 (2.9%)

* *n (%).*

Discussion and conclusion remarks

Approximately 25% of newly diagnosed patients with bladder cancer presented as muscle invasive disease (1), and 2% as locally advanced (pT4) (20), with high probability of manifesting irritative *lower urinary tract symptoms* (LUTS), suprapubic pain and gross hematuria. Therefore, advanced bladder cancer can be significantly disabling and can worsen patients' quality of life.
EAU guidelines recommend radical cystectomy as the first treatment option1, mainly because of its' superiority regarding *overall survival* (OS) and *cancer specific survival* (CSS) when compared to bladder sparing treatments such as radiotherapy, TURBT-T or chemotherapy alone (21). Moreover, these treatments could actually make patients' quality of life deteriorate by exacerbating the local symptoms or causing treatment-related symptoms (e.g. actinic colitis) (22). On the contrary, if left untreated, 38% of the patients will present metastasis within 6 months of initial diagnosis (21).
Radical cystectomy was first described in 1940s and was associated with extremely elevated perioperative mortality, up to 33% (23), but few decades later mortality rates stabilized at 2-5% (3).
Some authors described up to 13.7% mortality rates during early postoperative period for frail patients (24), whilst some tertiary centers report extremely low rates, as low as 0.5%, that could be explained by patient selection

Table 4.
Descriptive characteristics of 34 patients treated with extraperitoneal cystectomy and ureterocutaneostomy from October 2018 to August 2020, stratified by complications.

Characteristics	**Complication**		**P-value** **
	No, n = 14 *	**Yes, n = 19** *	
Age, (years)	76.7 (72.3, 80.0)	77.8 (71.8, 80.5)	> 0.9
BMI, (kg/m^2)	25.0 (23.1, 26.8)	27.0 (25.0, 30.5)	0.082
Preoperative creatinine, (mg/dL)	1.27 (1.13, 1.48)	1.40 (1.19, 1.76)	0.3
Preoperative albumin, (g/dL)	3.11 (2.62, 3.79)	3.30 (2.80, 3.71)	0.7
MUST score			0.6
0	7 (50%)	9 (47%)	
1	6 (43%)	6 (32%)	
2	1 (7.1%)	4 (21%)	
ASA score			0.11
1	1 (7.1%)	0 (0%)	
2	5 (36%)	3 (16%)	
3	7 (50%)	16 (84%)	
4	1 (7.1%)	0 (0%)	
RAI	26.5 (25.0, 28.8)	30.0 (27.5, 33.0)	0.027

* *Median (IQR); n (%).* ** *Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test.*

bias, although it is a well-known fact that high-volume centers tend to have less peri- and postoperative complications (25). Furthermore, one study revealed that the probability of undergoing radical cystectomy for elderly patients is five-fold lower than for younger ones (26).
Consequently we asked ourselves the following questions. Should we deny a surgical option to patients in our cohort who were considered frail?
Could we instead treat those frail patients with extraperitoneal cystectomy followed by ureteral diversion to the abdomen wall that is reputed as the simplest form of urinary diversion with lower complication rates, morbidity and mortality (27)?
Furthermore, when *Longo et al.* assessed the quality of life in patients treated with ileal conduit and UCS using the Bladder Cancer Index, patients reported the same level of discomfort equally in both groups (28).
In our study we confirmed findings previously reported in the literature. In fact, in our cohort median blood loss and operative time were reduced, when compared to reports of intraperitoneal radical cystectomy with bowel diversion. *De Nunzio et al.* described even more reduction in operative time, but that could be due to different surgical technique or more experienced second surgeon (29).
The association between some preoperative characteristics of the patients and rates of complications were previously reported in the literature (30, 31).
The association between perioperative hypoalbuminemia and risk of wound infection was also reported by other authors (32). Similar observations were made for BMI and septicemia and for anemia, ASA > 3 and RAI score > 25 and development of deep subfascial wound infection with evisceration or needing readmission.
Moreover, in our cohort, there were no complications such as anastomotic leakage, hematomas or mechanical bowel obstructions, and at the end of perioperative period we did not observe any death although we had one death in the early postoperative period.
Due to this experience, we believe that performing an extraperitoneal cystectomy with UCS and implementation of the ERAS protocol, the risk of intestinal complications such as paralytic ileus, gastroparesis and electrolytic imbalance are significantly lowered, as well as likelihood of urinary fistulas. Where the surgery was only palliative, we avoided lymphadenectomy and, thus, lymphocele and all the related consequences.
These are the main reasons why we consider extraperitoneal cystectomy with UCS a safer surgical technique when treating frail patients.
However, our study is not without limits. Firstly, it is a retrospective study on a small cohort of patients. Secondly, some patients may have not undergone correct staging of disease as they did not undergo the lymphadenectomy. Furthermore, patients, although all considered frail, were not homogeneous. They, in fact, differed in age, clinical manifestation of disease, BMI, stage, laboratory findings, malnourishment risk and not all patients underwent ERAS protocol. Furthermore, there is no control group due to the fact that this surgery is reserved only for the patients that would otherwise be considered unfit for surgery.
However, the aim of this study was to evaluate the safety of extraperitoneal cystectomy with UCS in frail patients, and it is also the main reason why having a more homogeneous cohort is difficult, if not impossible.
Nevertheless, this technique should be evaluated on larger cohorts.
We do believe it is our duty to evaluate patients in more holistic manner in order to choose the right surgical approach. We should inform patients about the risks we are taking and use all preoperative tools at our disposal in order to prepare patients for this battle (e.g. could we administer intravenous albumin?).
And while for the 'fit-for-surgery' patients there is continuously more evidence for robotic-assisted radical cystectomy (33), we do believe that the 'frail patients' category is somehow forgotten. Open extraperitoneal cystectomy with UCS could be considered as a surgical option for those who are categorized as 'unfit', especially if it could be radical and ensure patients a disease-free residual life.
We do, however, have to perform an accurate preoperative evaluation and the surgery should be performed by an experienced surgeon who is comfortable with extraperitoneal approach to the bladder.

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Correspondence

Rafaela Malinaric, MD (Corresponding Author)
rafaela.malinaric@gmail.com

Guglielmo Mantica, MD
gugliemo.mantica@gmail.com

Federica Balzarini, MD
balzarini.federica90@gmail.com

Carlo Terrone, MD
carlo.terrone@med.unipo.it

San Martino Hospital, University of Genoa, Genoa (Italy)

Massimo Maffezzini, MD
massimo.maffezzini@gmail.com

Department of Urology, Hospitals of Legnano and Magenta, Milan (Italy)