Original Article

Outcomes of radical cystectomy in pT4 bladder cancer frail patients: A high-volume single center study

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Abstract

Objectives: This study aims to evaluate the effect of frailty in patients undergoing radical cystectomy (RC) for locally advanced bladder cancer. **Methods**: In this retrospective, single center study we evaluated 51 patients with pT4 bladder cancer treated with radical cystectomy between 2016-2020. Patient frailty was assessed with the Clinical Frailty Scale (CFS). Furthermore, six separate parameters (early mortality index within 30 days after surgery, death after one year, length of stay, respiratory complications, readmission index, total hospital charges) were also evaluated. The patients were categorized on three groups (Group 1, 2, 3) based on the CFS. **Results**: A total of 51 pT4 RC patients were included in the study. Mean age was 75.6 years. Early mortality rate at 30 days after surgery was low all the groups. One year mortality rate was higher in Group 2 (22%) and 3 (69%). The length of stay and the number of patients with respiratory complications were also higher in the frailer groups. 30 days readmission rate was 22% in Group 2 and 38% in Group 3. **Conclusions**: Preoperative frailty is associated with worse postoperative results after RC. CFS is an objective tool for patient risk stratification and can predict postoperative complications and mortality.

Keywords: Outcomes of radical cystectomy in pT4 frail patients, Radical cystectomy in frail patients, Radical cystectomy in pT4 patients, Radical cystectomy in pT4 and frail patients

Introduction

Urothelial carcinoma is the ninth most common cancer worldwide and the second most common malignancy of the urogenital system. At diagnosis 20-25% of bladder cancer patients are muscle invasive and thus face a high risk of progression and metastasis[1]. Radical cystectomy (RC) with pelvic lymph node dissection and urine diversion is currently the gold standard surgical treatment, with the best-proven oncologic results[2]. In spite of improvements in surgical techniques and perioperative care, RC is still associated with a high rate of complications and high morbidity and mortality.

The incidence of urothelial cancer increases with age. Therefore, in developed countries where life expectancy is gradually increasing, it is expected that the number of elderly patients with such cancer will increase in parallel

in the future[3]. Although several studies claim that rising age is associated with higher RC mortality and morbidity, chronological age on its own does not always reflect the overall health status of patients with urothelial cancer who

Patient characteristics	Group 1 (CFS 1-3)	Group 2 (CFS 4-6)	Group 3 (CFS 7-9)
Patients (%)	12 (24)	23 (45)	16 (31)
Age yrs (mean, range)	72.5 (61-78)	75.5 (69-81)	78 (71-83)
Male gender pts	9	19	13

Table 1. Clinical Frailty Scale Groups and patient characteristics.

have undergone or are about to undergo surgery related to their disease[4]. Determination of frailty is an accurate method of assessing the patients' health and therefore the likelihood of postoperative complications[4]. Frailty is defined as a biological syndrome of decreased physiologic reserve and resistance to stressors causing vulnerability to adverse outcomes[5]. Possible factors related to frailty include malnutrition, weight loss, low activity, weakness, and catabolic status. Although it is a predominantly geriatric condition, it may also affect younger patients. By definition, frailty is a dominant factor in patient health status as it affects physical reserves and compromises recovery after surgical procedures[6]. Based on the aforementioned, frailty could be defined as a valuable tool for predicting perioperative risk, especially if we consider that frailty has a significant impact on cancer patients, as it has been shown to reduce physical reserves and prolong recovery after surgery or systemic treatment[4]. Therefore, several weakness scores have been introduced for the specific assessment of this condition and the complete prediction of the risk of adverse outcomes in major surgery candidates[7].

To date, the effect of frailty on RC postoperative outcomes has not yet been thoroughly investigated. In addition, although several methods have been developed to measure patient frailty, the best in terms of both prognosticity and ease of use has not yet been identified. In our study we conducted an assessment of frailty in the subpopulation of pT4 RC patients in our high-volume cystectomy center. The aim of this study is to present and quantify the effect of frailty in this subgroup of poor prognosis patients with MIBC who undergo RC.

Materials and Methods

In this retrospective, single center study we collected data from a total of 54 pT4 patients treated with open RC for MIBC in our high-volume cystectomy center between the years 2016 and 2020. Assessment of frailty was based on Clinical Frailty Scale, Version 2.0 (included in the 2021 EAU Guidelines)[8].

All RCs with lymph node dissection were performed by experienced high volume surgeon and in all patients the chosen method of urine diversion was uretero-dermostomies. Frailty assessment was supervised by an anesthesiologist specialized to preoperative screening and was based on

the validated Clinical Frailty Scale (CFS), Volume 2, in order to assess physical, mental and social frailty. Patient data, including medical history and laboratory tests were examined in relation to CFS. Extent medical history was recorded, and all patient comorbidities were documented. CFS divides patients into 9 categories. Patients included in category 1 are described as very fit while patients in category 9 as terminally ill. In our analysis all cases were classified into three groups based on the CFS. Group 1 included patients of CFS 1-3 while Group 2 included patients with CFS 4-6 and Group 3 patients with CFS 7-9. Each group was examined in relation to early mortality rate (EMR) within 30 days after surgery, one year mortality rate (YMR), length of stay (LOS), respiratory complications, readmission rate at 30 days and total hospital charges due to surgical-site infection.

Exclusion criteria

Patients with history of radiotherapy in the pelvis, concomitant upper tract urothelial cancer, incomplete follow up regarding the post-surgery parameters evaluated, as well as cases in which the bladder was not removed, were excluded from the study. In total 3 patients were excluded from the study, one for each of the above-mentioned reasons. As a result, a total of 51 patients were finally included in our study.

Results

A total of 51 pT4 RC patients were included in the analysis. Mean age was 75.6 years, and the majority of patients (80.4%) were males (41) with men to women ratio at 3.7:1.

More specifically, Group 1 included 12 patients with a mean age of 72.5 years. Group 2 consisted of 23 patients with a mean age of 75.5 years and Group 3 included 16 patients with a mean age of 78 years (Table 1). EMR at 30 days after surgery was low for all groups with only one death recorded in the first postoperative month in Group 3. In Group 1 only one patient died at 12 months after surgery in comparison to 5 patients in Group 2 (22%) and 11 patients in Group 3 (69%). The LOS was 8 days in Group 1, 13 days in Group 2 and 17 days in Group 3. Furthermore, only one patient in Group 1 developed respiratory complications in comparison to 14 and 15 patients in Group 2 and 3, respectively. Finally, the 30 days readmission rate was much

Comparison of the results of the 3 groups	Group 1 (n=12)	Group 2 (n=23)	Group 3 (n=16)
Early Mortality Rate, pts (%)	0	0	1 (6)
Year Mortality Rate, pts (%)	1 (8.3)	5 (22)	11 (69)
Length of Stay, days, (mean, range)	8 (7-11)	13 (9-21)	17 (10-33)
Respiratory Complications, pts (%)	1 (8)	14 (61)	15 (94)
30 days Readmission Rate, pts (%)	0	5 (22)	6 (38)

Table 2. Results between different patient age groups.

higher in Group 2 (22%) and Group 3 (38%) compared to no patient readmitted in the first postoperative month in Group 1 (Table 2).

Discussion

Based on our results, patients with higher frailty index are associated with worse postoperative results after RC. The length of stay and the 30 days readmission rate as well as the number of patients presented respiratory complications and the one year mortality rate were higher in the frailer patients. As a result, it is becoming increasingly important to identify frail patients with increased risk of severe complications and mortality during the perioperative period.

The expansion of the elderly population worldwide is associated with vulnerability, and this ageing population is adding increasing pressure on urological surgery[9]. Meanwhile, RC is considered a procedure with considerable risks and postoperative complications. Mortality occurs in 1.5% of patients within 30 days of primary surgery while 90-day mortality rate is 4.7%. Respectively, the surgeon has to cope with a high rate of morbidity, as 58% of patients will experience at least one complication within 90 days after RC. The most common RC complications are gastrointestinal (29.0%) and infectious (14,1%) diseases[10,11]. Moreover, it must be highlighted that complications ratio is strongly associated with the surgical procedure and the type of urinary diversion. Most of the studies agree that complications are less frequent after cutaneous ureterostomy compared to ileal conduit while mortality rate is similar among the two techniques[12]. Based on the upon it is of the utmost importance to define a method to assess patients' perioperative risk and predict outcomes after the surgical procedure especially in the subgroup of poor prognosis pT4 patients which is associated with 44% disease-free survival , 5 years after the RC[13].

Frailty is a predominantly geriatric condition that may be closely related to malnutrition, low activity, and catabolic balance[5]. It has a significant impact on cancer patients, as it has been shown to reduce physical reserves and prolong recovery after surgery or systemic treatment[4]. The study by Ethun et al. reported that 8% of patients undergoing RC were diagnosed as frail and 31% as pre-frail, a condition used to describe patients diagnosed with some components of a frailty measure but not enough to meet the defined frailty cut-off[14]. As age increases frailty also rises with results from studies indicating that between 80 and 89 years old, frail and pre-frail patients increase to >60%[15]. Therefore, the use of a reliable and simple frailty index in our study arises as an effective tool in the preoperative setting with potential benefits in our RC postoperative results, especially in the poor prognosis pT4 subgroup of patients where the percentage of frailty seems to be higher.

There is no commonly accepted frailty assessment scoring system. Different methods and indexes have been used in the past years. In our analysis the Clinical Frailty Scale, Version 2.0 (included in the 2021 EAU Guidelines) was implemented[8]. It derives from the Canadian Study of Health and Aging (CSHA), stratifies patients in nine categories-scales of frailty and is easy to use in everyday clinical practice.

A variety of studies have highlighted the utility of frailty as a prognostic factor of perioperative morbidity and mortality. Recently Palumbo et al conducted a large retrospective study investigating the importance of frailty assessment among patients undergoing RC. Frailty seemed to be a strong and independent negative predictor regarding overall complications and other parameters examined[16,17]. Results of our retrospective study agree with these of previous studies and systematic reviews that, patients with higher frailty index present worse postoperative results after RC.

Our results varied a lot between the frail and non-frail groups of patients. This fact underlines the importance of using a standardized frailty assessment tool as a method of patient classification. In our study frailty in the subpopulation of pT4 RC patients played an important role in patient prognosis in the perioperative and postoperative setting.

Conclusions

The absence of a widely accepted definition of frailty and the lack of standardization among studies underline the need of further evaluation of frailty as an emerging reliable predictive factor in clinical practice. Moreover, multimodal prehabilitation programs that may potentially improve or reverse weakness before RC should also be considered

and implemented on a large prospective scale in order to optimize clinical outcomes and improve the perioperative prognosis of RC patients. In our study the status of preoperative frailty is associated with worse postoperative results after RC. CFS emerged as a good and objective tool for patient risk stratification with prognostic advantages concerning postoperative complications and post-RC mortality. PT4 patients can benefit from the implication of such a frailty screening tool regarding patient counseling and the optimization of treatment modalities.

Ethics approval

The study was approved by the Ethics Committee of the General Hospital of Athens, "G. Gennimatas". The study complied with the principles of Declaration of Helsinki for protection of human rights.

Consent to participate

All patients were informed in detail by the treating physician for inclusion in the study and signed an informed consent prior to participation.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30.
2. Witjes JA, Lebret T, Compérat EM, et al. Updated 2016 EAU Guidelines on Muscle -invasive and Metastatic Bladder Cancer. Eur Urol 2017;71(3):462-475.
3. Fonteyne V, Ost P, Bellmunt J, et al. Curative treatment for muscle invasive bladder cancer in elderly patients: a systematic review. Eur Urol 2018;73(1):40–50.
4. Ethun CG, Bilen MA, Jani AB, et al. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67(5):362–377.
5. Parikh N, Sharma P. Frailty as a prognostic indicator in the radical cystectomy population: a review. Int Urol Nephrol 2019;51(8):1281–1290.
6. Ornaghi PI, Afferi L, Antonelli A, et al. Frailty impact on postoperative complications and early mortality rates in patients undergoing radical cystectomy for bladder cancer: asystematic review. Arab J Urol 2021;19(1):9–23.
7. Hanna K, Ditillo M, Joseph B. The role of frailty and prehabilitation in surgery. CurrOpin Crit Care 2019;25(6):717–722.
8. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. Cmaj 2005 173:489.
9. Kostakopoulos NA, Karakousis ND. Frailty assessment and postoperative complications in urologic oncology operations. J Frailty Sarcopenia Falls 2020; 5(3): 57–61.
10. Hautmann RE, Hautmann SH, Hautmann O. Complications associated with urinary diversion. Nat Rev Urol 2011;8(12):667-77.
11. Maibom SL, Joensen UN, Poulsen AM, et al. Short-term morbidity and mortality following radical cystectomy: a systematic review. BMJ Open 2021;11(4):e043266.
12. Korkes F, Fernandes E, Gushiken FA , et al. Bricker ileal conduit vs. Cutaneous ureterostomy after radical cystectomy for bladder cancer: a systematic review. Int Braz J Urol 2021;47.
13. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, Skinner E, Bochner B, Thangathurai B, Mikhail M, Raghavan D, Skinner DG. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin OncoL 2001;19(3):666-75.
14. Ethun CG, Bilen MA, Jani AB, et al. Frailty and cancer: implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67(5):362–377.
15. De Nunzio C, Cicione A, Izquierdo L, et al. Multicenter analysis of postoperative complications in octogenarians after radical cystectomy and ureterocutaneostomy: the role of the frailty index. Clin Genitourin Cancer 2019;17(5):402-407.
16. Palumbo C, Knipper S, Pecoraro A, et al. Patient frailty predicts worse perioperative outcomes and higher cost after radical cystectomy. Surg Oncol 2020;32:8-13.
17. Burg ML, Daneshmand S. Frailty and preoperative risk assessment before radical cystectomy. Curr Opin Urol 2019;29(3):216-219.