



The Importance of a Multidisciplinary Approach for Radical Cystectomy: The GRACE-M Project

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Backgrounds: ERAS protocols result in inadequate assessment of comorbidities and frailties. In this study we analyze a new multidisciplinary clinical pathway inspired by the ERAS protocols, the GRACE-M project (designed for patients requiring Radical Cystectomy and focused on frailties and nutritional status), comparing these patients to a population of Radical Cystectomy patients not enrolled in this pathway.

Methods: This study is a comparison between a group of patients enrolled in the GRACE-M pathway, a single-center ongoing prospective cohort study, and a group of patients who received Radical Cystectomy without being recruited in the pathway. We did a non-randomized pre-post cohort study. The primary outcome was complications' rate at 30 and 90 days and their severity, the secondary outcomes were mortality and readmission rate. We performed a multinomial logistic regression to evaluate the differences in outcomes between the two groups.

Results: Overweight patients were more likely to have complications at 30 days (OR 2.39, *P*-value 0.04). Female patients (OR 0.06, *P*-value 0.02) and GRACE-M patients (OR 0.1, *P*-value 0.01) had reduced odds to experience a major complication (Clavien-Dindo>2) at 90 days. The main limitations of the study can be found in the limited number of patients and the difference between the enrollment of the two groups, since the control group is made of patients who underwent Radical Cystectomy prior to the initiation of the GRACE-M protocol.

Conclusion: In this study we analyzed a new multidisciplinary pathway for Radical Cystectomy. Our findings support the adoption of the GRACE-M protocol for candidates for Radical Cystectomy, especially due to a reduced risk of a major complication at 90 days. This article can serve as a starting point for further exploration of this topic.

Keywords: Bladder cancer; Radical cystectomy; ERAS; Multidisciplinary; Frailty; Nutritional status.

Introduction

Bladder cancer is the 10th most diagnosed cancer, with a worldwide incidence rate of 9.5 for men and 2.4 for women^[1]. Depending on the depth of invasion of the neoplasm it is possible to distinguish between non-muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC). The first-line treatment for non-metastatic MIBC and high-risk NMIBC is radical cystectomy (RC) with pelvic lymphadenectomy and urinary diversion -orthotopic neobladder, ileal conduit or ureterocutaneostomy- possibly preceded by neoadjuvant chemotherapy^[2-4]. RC is a challenging procedure, with a significant impact on patients' quality of life^[5,6].

the complications' rate at 30 and 90 days after RC can be as high as 80% (Pfail et al. in their analysis found that the rate of any complication can reach 84.9%) and the mortality rate at 30 and 90 days is 2.1% and 4.7% respectively^[7,8]. These outcomes have improved following the introduction of ERAS protocols^[9]: Enhanced Recovery After Surgery (ERAS) protocols are evidence-based, multimodal perioperative care pathways aimed at reducing surgical stress and improving postoperative recovery. They combine standardized interventions before, during, and after surgery - such as optimized anesthesia, early mobilization, and early oral intake- to decrease complications, shorten hospital stay, and enhance patient outcomes. According to several studies, adhering to ERAS standards significantly reduces time-dependent postoperative indicators, with no difference in terms of cancer-related indicators^[10,11]. Nevertheless, it has been observed that patients differ in their ability to comply with ERAS standards due to factors not accounted for in these protocols, such as sarcopenia and frailty, which have been found to be associated with adverse outcomes after RC^[12,13]. Despite the recommendations of many

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guidelines to include the assessment of nutritional status and frailty in the preoperative routine for patients undergoing major surgery, and the evidence of the impact on patient outcomes following major surgery^[14-16], these factors are rarely evaluated across institutions. Recently, several frailty scores have been devised to predict outcomes after major surgery but, due to the plethora of scoring systems, comparing frailty between studies using different scores is difficult. Similarly, increasing attention is being given to the assessment of nutritional status in these patients. Newly developed evaluation scores- based on blood test parameters—are being used with growing frequency, and their values have been shown to correlate with different risks for complications after radical cystectomy^[17]. Therapeutic strategies involving nutritional interventions are also central, such as encouraging the early return to enteral feeding or adopting specific dietary regimens as immunonutrition^[18,19]. Given the importance of these parameters, we developed the GRACE-M project (Global Radical Cystectomy Evaluation and Management), a multidisciplinary pathway dedicated to patients undergoing radical cystectomy for bladder cancer. Based on ERAS principles, the GRACE-M project also focuses on the assessment of patients' nutritional status and frailty as key components of the surgical care process^[20]. The pathway includes a series of multidisciplinary meetings, where joint decisions are made by the Core Team throughout the entire clinical course, while also coordinating with the patient and their caregivers. The management of each clinical case begins at the time when the patient is considered a candidate for RC and continues at regular intervals until the end of the designated 1-year follow-up period. In this article we aim to conduct a preliminary analysis of the data from this project, evaluating oncological outcomes and complication rates in patients who had reached at least 90 days of follow-up, comparing these results with those from a control population with similar characteristics- patients who underwent radical cystectomy for bladder cancer at our institution, with a minimum of 90 days of follow-up- not enrolled in a multidisciplinary care pathway.

Materials and methods

Study design

The GRACE-M pathway is a prospective, observational, single-center cohort study with 1-year follow-up. Ethical approval was obtained from the independent ethics committee of the IRCCS Humanitas Research Hospital (N° 3317; 18/11/2022). Written informed consent was obtained from all patients at the time of inclusion. The multidisciplinary pathway includes a series of scheduled appointments (before and after surgery) and in-hospital monitoring of anthropometric and blood parameters, along with a follow-up phone call by the case manager 15 days after discharge. At each appointment, an evaluation of the patient's nutritional status and frailty profile are performed. Our dedicated frailty questionnaire is the Functional Limitation and Geriatric Syndromes Frailty Questionnaire (FLIGS-FQ), a patient-reported measure used as a screening tool and as a health outcome measure during patient follow-up. All enrolled patients were assessed through a 24-hour recall, measuring their caloric, protein and fluid intake. During the appointments, potential clinical interventions are defined based on the available data, which is why the initial intake meeting is crucial, as it represents the moment in

which the patient's surgical eligibility for RC is confirmed or excluded^[21]. All the steps of this pathway are discussed with the patient and their caregivers, to share the risk-benefit ratio of the surgical approach compared to alternative options, respecting the patient's preferences while aiming for the best possible outcome in terms of quality of life^[20]. In the GRACE-M protocol we included all patients with a histological diagnosis of bladder cancer, who were candidates for elective surgery. Patients with a benign disease were excluded, as well as those needing urgent RC, and cases where the time between surgical indication and intervention was insufficient to ensure a pre-operative multidisciplinary assessment per protocol. The decisional pathways of the protocol (before and after surgery) are shown in detail in Fig. 1 and Fig. 2.

Study population

We retrospectively analyzed data belonging to patients who underwent Radical Cystectomy with pelvic lymphadenectomy between 2018 and 2024. Patients were identified using the ICD10 specific code for radical cystectomy. We conducted a non-randomized pre-post cohort study with two groups: a control group, which included patients who underwent RC and were managed according to standard surgical care, and the GRACE-M group, which included patients who were enrolled in the project and therefore underwent RC after being assessed by our multidisciplinary team. In this paper we included patients who underwent radical cystectomy for bladder cancer (both MIBC and NMIBC) and for whom adequate documentation was available regarding medical history and hospital stay; to avoid follow-up imbalance between the two groups, we focused on the first 90 days of follow-up. We excluded patients who underwent radical surgery for benign conditions, with inadequate follow-up or with insufficient data about personal history, hospital stay or follow-up.

All patients underwent Radical Cystectomy at our institute, IRCCS Humanitas Research Hospital, a Joint Commission International (JCI)-accredited tertiary teaching hospital and a national Italian referral center for urologic cancer surgery.

Covariates

The covariates integrated in the analysis include sociodemographic, clinical and pathological variables: age, sex, BMI, comorbidity burden -defined by the Charlson-Deyo Comorbidity Index (CCI)-, ACS NSQIP surgical risk score before surgery, personal history of bladder cancer, histological diagnosis from the latest endoscopic procedure, neoadjuvant chemotherapy (including the number of cycles received^[22]), surgical parameters, histological diagnosis from the Radical Cystectomy, and hospital stay.

Outcomes

The primary outcome of the study was the complications' rate at 30 and 90 days, and their severity according to the Clavien-Dindo score. The secondary outcomes were mortality and readmission rate.

Statistical analyses

The statistical analysis of the quantitative data was carried out us-

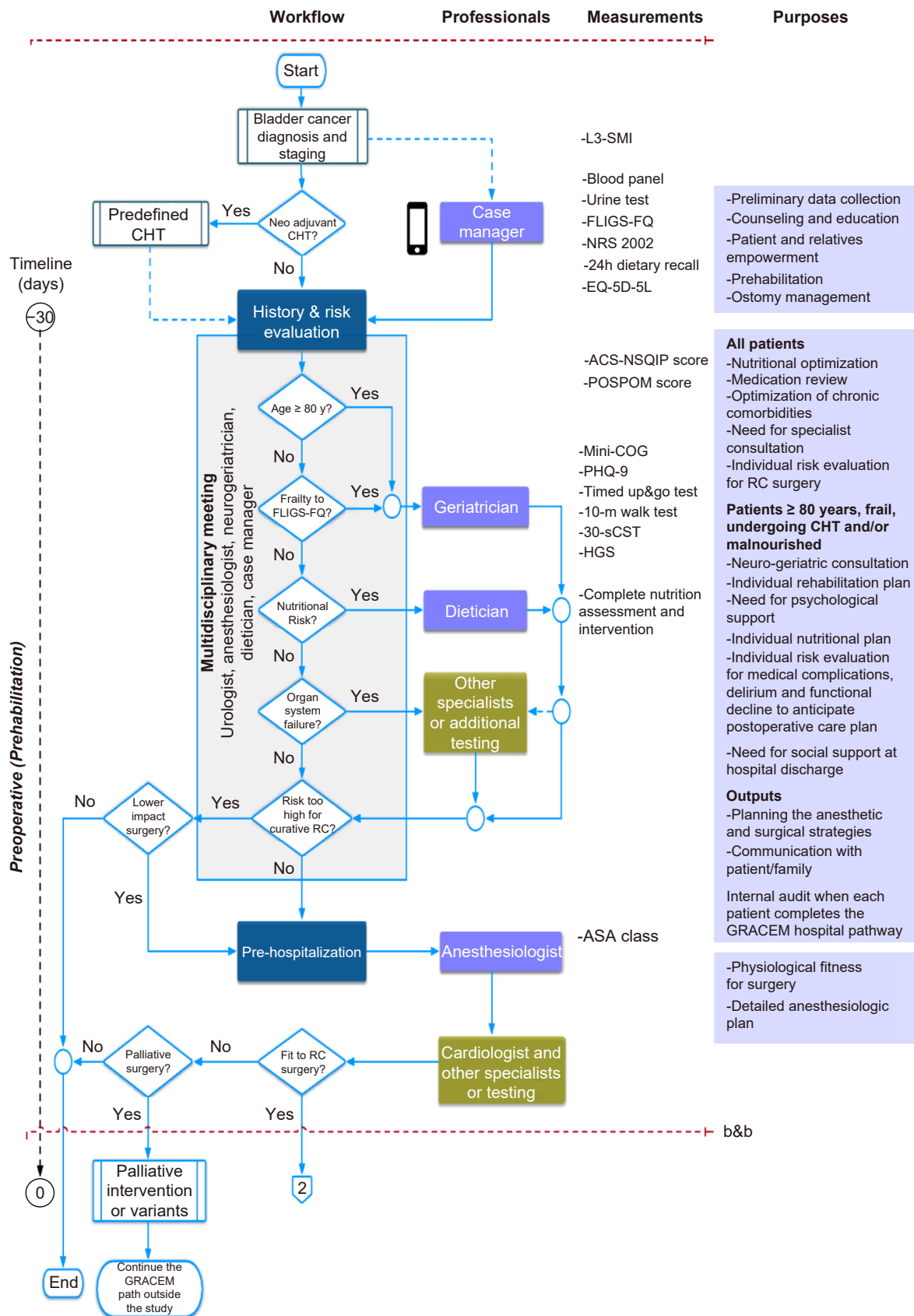


Fig. 1. The pre-operative pathway of the GRACE-M protocol.

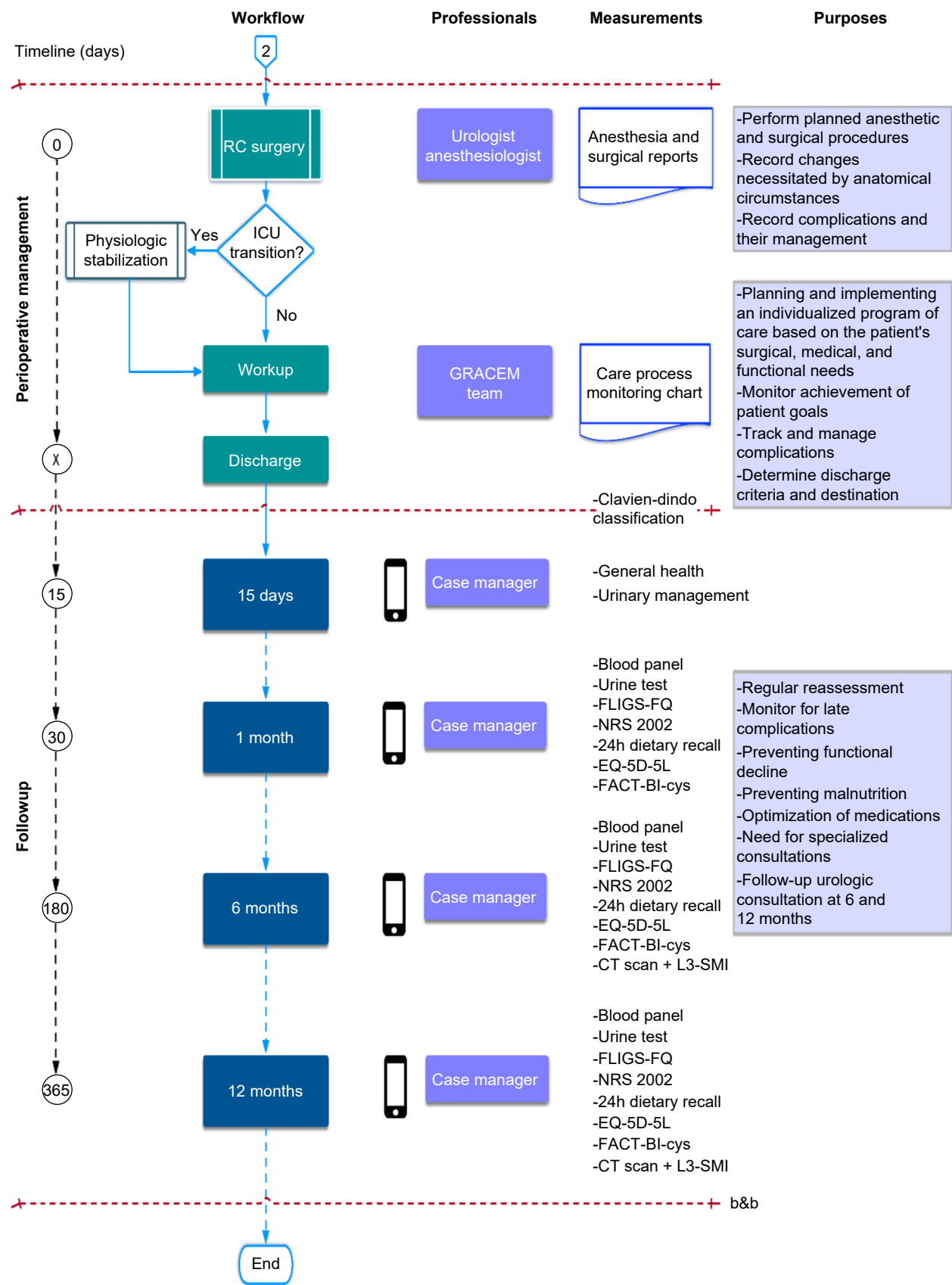


Fig. 2. The post-operative pathway of the GRACE-M protocol.

ing STATA/SE, version 18.0 (Stata Corp). Descriptive statistics were used to summarize patients' demographics before surgery, tumor characteristics and surgical parameters. Categorical variables were analyzed using the chi-square test. Continuous variables were expressed as median values with interquartile ranges (IQRs). We performed a multinomial logistic regression to evaluate predictors of outcomes. In the interpretation of the results, the convention was adopted that a value of $P < 0.05$ was considered indicative of statistical significance and all confidence intervals (CIs) were reported at the 95% level.

Results

Baseline characteristics

A total of 139 patients who underwent Radical Cystectomy between 2018 and 2024 were included: the control group consisted of 99 patients who underwent radical surgery between 2018 and 2021, while 40 patients who underwent RC between 2023 and 2024 were included in the GRACE-M protocol. We excluded all patients from 2022 due to a lack of post-surgical follow-up data (Fig. 3).

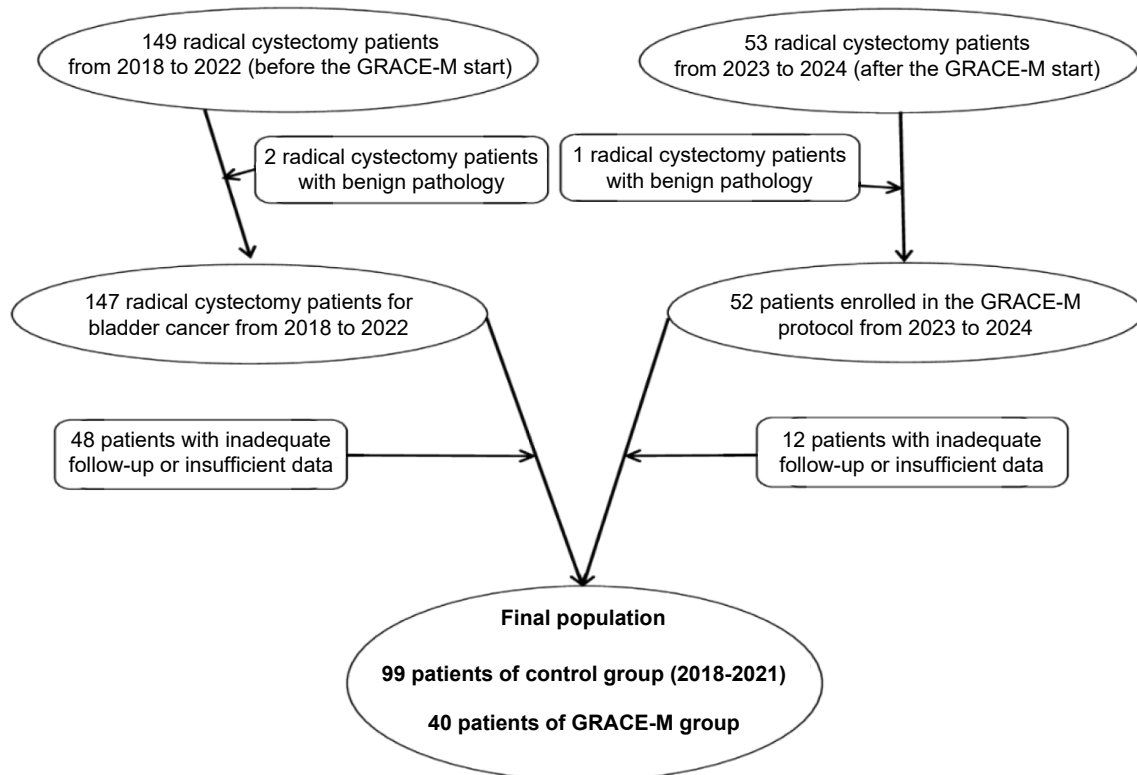


Fig. 3. Flow diagram of patients' selection for control and GRACE-M group.

The median age was 72 in the control group and 71 in the GRACE-M group; in both groups, most patients were male. The median BMI before surgery was 25.5 in the control group and 26.5 in the GRACE-M group. The two groups had similar comorbidity burden- a median CCI score of 5- and risk percentages according to the ACS NSQIP (Table 1).

In most cases they had a pure urothelial type (70.5% in the control group and 80.5% in the case group). 66.3% of the control patients had a MIBC diagnosis, compared to 65% of the case group. Carcinoma in situ (CIS) was diagnosed at similar rates in the two groups. 19.2% of the control group and 22.5% of the GRACE-M group received neoadjuvant chemotherapy prior to radical surgery, with a median of 3 administered cycles (Table 2).

Radical cystectomy data

All patients in the control group underwent open surgery, while 3 patients in the GRACE-M group underwent robotic RC. The GRACE-M group showed higher blood loss and longer surgical procedure duration compared to the control group. In the control

group, the most frequently used urinary diversion was the ileal conduit, performed in 51 patients, followed by ureterocutaneostomy and ileal neobladder. In the case group, the most common urinary diversion was ureterocutaneostomy, performed in 17 patients, followed by neobladder and ileal conduit. After surgery, approximately 14% of patients in the control group required admission to the intensive care unit, whereas in the case group this occurred in 10% of cases. Following radical cystectomy, all control patients had a nasogastric tube placed, while only 12.5% of the patients enrolled in the GRACE-M project did. Finally, the two groups had a comparable length of hospital stay (Table 3).

We observed a greater histotype heterogeneity in the control group, with histological variants diagnosed in 32.3% of cases (pure urothelial histotype in 26.2%, CIS in 19.2%, and negative final pathology -T0N0- in 22.2%); the GRACE-M group showed a predominance of pure urothelial histotype in 47.5% of cases (25% histological variants, 7.5% CIS, and 20% negative final pathology-T0N0). The GRACE-M group also showed a slightly higher frequency of more invasive tumor forms, with either a negative pathology report or a non-muscle-invasive tumor found

Table 1. Baseline characteristics of the two populations.

Variable		No GRACE-M (n = 99)	GRACE-M (n = 40)	P-value
Sex(%)	Female	16 (16.2)	6 (15)	0.87
	Male	83 (83.8)	34 (85)	
Age at surgery(%)		72 (65–77)	71 (59–76.5)	0.36
Smoking status(%)	No smoker	19 (19.2)	5 (12.5)	
	Previous smoker	33 (33.3)	13 (32.5)	
	Active smoker	47 (47.5)	22 (55)	
BMI at surgery(%)		25.5 (23–27.7)	26.5(23.6–31)	0.11
CCI at surgery(%)		5 (4–7)	5 (4–7)	0.53
ACS NSQIP surgical risk(%)	%Any complications	25.5 (20.9–29.3)	27.5 (23.6–32.6)	0.079
	%Serious complications	22.2 (18.8–26.1)	23.5 (21.1–28)	0.13
	%Readmission	18.3 (16–22.5)	19.3 (17.1–25.6)	0.09

Table 2. Patient's data from the last endoscopic procedure.

Variable		Control	GRACE-M
Grade from TUR	LG	0%	0%
	HG	100%	100%
Stage from TUR	Ta	9.2%	12.5%
	T1	24.5%	22.5%
	T2	66.3%	65%
Histology from TUR	Urothelial	70.5%	80.5%
	Non urothelial	29.5%	19.5%
CIS from TUR	No	81.44%	77.8%
	Yes	18.56%	22.2%
Neoadjuvant chemotherapy		19.2%	22.5%

Table 3. Radical cystectomy's difference between the two population.

		Control	GRACE-M	P-value
Type of surgery	Open	100%	92.5%	
	Robotic	0%	7.5%	
Type of urinary diversion	UC	32.3%	42.5%	
	IC	51.5%	25%	
	NB	16.2%	32.5%	
Estimated blood loss (cc, median)		350, IQR 250–550	500, IQR 400–725	0.083
Operating room time (min, median)		305, IQR 255–342	330, IQR 276.5–365	0.074
Nasogastric tube	No	0%	87.5%	
	Yes	100%	12.5%	
Intensive care admission	Yes, scheduled	12%	5%	
	Yes, not scheduled	2%	5%	
	No	86%	90%	
Length of stay (days, median)		11, IQR 9–15	11.5, IQR 9–15	0.22

in 42.5% of cases, while in the remaining 57.5% the tumor invades beyond the muscular layer, involves regional lymph nodes, or presents with a positive surgical margin. In the control group such invasive forms were observed in 51.5% of cases, while 48.5% of patients had either no residual tumor or a tumor that spared the muscular layer.

Results after the radical cystectomy

We analyzed the complications' rate dividing them into complications at 30 days and 90 days. We classified the complications'

severity using the Clavien-Dindo system, defining as major complication every complication with a Clavien-Dindo score >2 (reporting only the worst score in case of more complications). We then performed a multinomial logistic regression to evaluate independent predictors of complications' rate and Clavien-Dindo score. We first analyzed independent predictors of complications and high Clavien-Dindo score at 30 days, finding that overweight patients had a statistically significant higher risk of having complications (OR 2.39, 95% CI 1.04–5.47, *P*-value 0.04) (Table 4).

Table 4. Multinomial logistic regression to assess independent predictors of complications' rate and Clavien-Dindo score at 30 days.

30 Days Complications			30 Days CD Score		
	OR (95% CI)	<i>P</i> .value		OR (95% CI)	<i>P</i> .value
No complications	Base outcome	Base outcome	CD 1-2	Base outcome	Base outcome
Complications			CD 3-4-5		
Age (years)					
<50	Ref.	Ref.		Ref.	Ref.
51–60	1.12 (0.08–15.7)	0.93		5.82 (0–.)	0.99
61–70	1.65 (0.13–21.12)	0.69		9.47 (0–.)	0.99
71–80	1.25 (0.09–15.9)	0.86		2.06 (0–.)	0.99
>80	2.19 (0.15–31.7)	0.56		7.47 (0–.)	0.99
Sex					
Male	Ref.	Ref.		Ref.	Ref.
Female	1.34 (0.45–3.97)	0.59		0.29 (0.02–3.3)	0.32
Smoke status					
No smoker	Ref.	Ref.		Ref.	Ref.
Smoker	1.32 (0.44–3.94)	0.62		0.25 (0.02–2.38)	0.23
Previous smoker	1.70 (0.62–4.63)	0.29		0.58 (0.09–3.46)	0.55
BMI					
Normal weight (18.5–24.9)	Ref.	Ref.		Ref.	Ref.
Underweight (<18.5)	2.74 (0.34–21.8)	0.34		1.96 (0.06–60.3)	0.70
Overweight (25–29.9)	2.39 (1.04–5.47)	0.04		1.10 (0.18–6.50)	0.91
Obesity (30–39.9)	1.49 (0.43–5.16)	0.52		0.27 (0.01–4.31)	0.36
Severe obesity (>40)	1.86 (0.09–35.4)	0.68		9.50 (0–.)	0.99
Cohort					
Control	Ref.	Ref.		Ref.	Ref.
GRACE-M	1.13 (0.50–2.54)	0.76		0.89 (0.21–3.70)	0.87

We then focused on the risk of overall and major complications at 90 days: female patients (OR 0.06, 95% CI 0.005–0.67, *p*-value 0.02) and GRACE-M patients (OR 0.1, 95% CI 0.01–0.63, *p*-value 0.01) had reduced odds of presenting a high Clavien-Dindo score (Table 5).

We finally analyzed mortality and readmissions trends. The control group experienced a total of 42 readmissions (42%) and 7 deaths (7%), while the GRACE-M group had 14 readmissions (33.3%) and 1 death (2.4%). We performed a multinomial logist-

ic regression to analyze independent predictors of death and readmission without finding statistically significant associations (Table 6).

Discussion

Our study found a statistically significant association between a reduced risk of a major complication at 90 days and the GRACE-

M group. Overall, overweight patients have a statistically significant higher risk of complications at 30 days. These findings highlight the importance of assessing the nutritional status and frailty profile of patients eligible for radical cystectomy, as these factors may impact their postoperative course^[13,23]. An accurate evaluation of patient frailty can provide valuable guidance for clinical decision-making, helping to determine the most appropriate surgical strategy- or even discouraging radical cystectomy in favor of less invasive alternatives^[21]. At the same time, accurately assessing nutritional status contributes to improving patient outcomes: anthropometric parameters^[24] or specific nutritional deficiencies^[15] are associated with reduced survival rates and an increased risk of complications in patients undergoing major surgery^[25-27], so these factors deserve more attention. We also think that maintaining direct communication with the patient plays a role in enhancing their overall well-being: this multidisciplinary pathway- which involves active engagement of both the patient and their caregivers, along with regular communication with the Case Manager- may enhance patient autonomy and awareness following radical cystectomy, and this continuous contact between the core team and the patient allows for improved monitoring of the postoperative course and any emerging complication. This article could also serve as a starting point for further analyses, integrating these assessments with specific tumor-related

parameters or therapeutic options to define a personalized care pathway for each patient. For instance, it could be valuable to explore how nutritional status and frailty interact with the histological variants of bladder cancer, which are known to have different clinical and prognostic implications^[28,29]; furthermore, while the importance of neoadjuvant chemotherapy in the treatment of MIBC is well established^[30], it would be interesting to investigate the compliance of frail or nutritionally deficient patients with this pharmacological treatment^[22].

This study has several limitations that must be acknowledged. The control group was evaluated retrospectively, which limits the reliability of the available data and introduces the potential for a selection bias due to the exclusion of patients with incomplete records. Furthermore, the control group underwent radical cystectomy during an earlier time period compared to the GRACE-M group, leading to possible differences in therapeutic decisions. Since we compared our results to a historical series, the risk of a Will Rogers bias has to be reported. All patients included in this study underwent radical cystectomy at our institution, so the population of patients who underwent RC may be not fully represented by our findings. The statistical significance of some outcomes may be affected by the limited total number of the patients included; larger prospective studies may help fully understand the clinical impact of the GRACE-M protocol.

Table 5. Multinomial logistic regression to assess independent predictors of complications' rate and Clavien-Dindo score at 90 days.

90 Days Complications			90 Days CD Score		
	OR (95% CI)	P.value		OR (95% CI)	P.value
No complications	Base outcome	Base outcome	CD 1-2	Base outcome	Base outcome
Complications			CD 3-4-5		
Age (years)					
<50	Ref.	Ref.		Ref.	Ref.
51–60	0.79 (0.05–11.5)	0.86		6.40 (0-.)	0.99
61–70	1.38 (0.10–18.3)	0.80		5.63 (0-.)	0.99
71–80	0.89 (0.06–11.7)	0.93		9.21 (0-.)	0.99
>80	1.21 (0.08–18.2)	0.89		3.83 (0-.)	0.99
Sex					
Male	Ref.	Ref.		Ref.	Ref.
Female	1.96 (0.61–6.26)	0.25		0.06 (0.005–0.67)	0.02
Smoke status					
No smoker	Ref-	Ref.		Ref.	Ref.
Smoker	0.50 (0.16–1.51)	0.22		7.32 (0.83–64.5)	0.07
Previous smoker	1.45 (0.54–3.91)	0.45		3.63 (0.61–21.5)	0.15
BMI					
Normal weight (18.5-24.9)	Ref.	Ref.		Ref.	Ref.
Underweight (<18.5)	0.30 (0.02–3.89)	0.36		3.93 (0-.)	0.99
Overweight (25–29.9)	1.68 (0.73–3.87)	0.22		1.06 (0.25–4.53)	0.93
Obesity (30–39.9)	0.79 (0.22–2.85)	0.73		4.86 (0.36–65.3)	0.23
Severe obesity (>40)	1.78 (0-.)	0.99		1.20 (0.01–75.2)	0.93
Cohort					
Control	Ref.	Ref.		Ref.	Ref.
GRACE-M	1.49 (0.63–3.48)	0.35		0.1 (0.01–0.63)	0.01

Table 6. Multinomial logistic regression to assess independent predictors of death and readmission rate.

Death			Readmission		
	OR (95% CI)	P.value		OR (95% CI)	P.value
No complications	Base outcome	Base outcome	CD 1-2	Base outcome	Base outcome
Complications			CD 3-4-5		
Age (years)					
<50	Ref.	Ref.		Ref.	Ref.
51–60	0.77 (0–.)	1		0.26 (0.02–3.65)	0.32
61–70	0.38 (0–.)	0.99		0.29 (0.02–3.63)	0.34
71–80	0.55 (0–.)	0.99		0.23 (0.01–2.83)	0.25
>80	0.96 (0–.)	0.99		0.23 (0.01–3.25)	0.27
Sex					
Male	Ref.	Ref.		Ref.	Ref.
Female	1.18 (0–.)	0.99		0.81 (0.26–2.49)	0.71
Smoke status					
No smoker	Ref.	Ref.		Ref.	Ref.
Smoker	0.98 (0.04–24.05)	0.99		0.81 (0.26–2.49)	0.71
Previous smoker	3.96 (0.28–55.2)	0.30		1.58 (0.58–4.31)	0.36
BMI					
Normal weight (18.5–24.9)	Ref.	Ref.		Ref.	Ref.
Underweight (<18.5)	1.04 (0–.)	0.99		1.77 (0.21–14.5)	0.59
Overweight (25–29.9)	0.45 (0.06–3.14)	0.42		1.48 (0.65–3.37)	0.34
Obesity (30–39.9)	7.74 (0–.)	0.99		0.92 (0.26–3.28)	0.90
Severe obesity (>40)	3.13 (0–.)	0.99		2.35 (0.12–44.9)	0.57
Cohort					
Control	Ref.	Ref.		Ref.	Ref.
GRACE-M	0.33 (0.02–4.55)	0.41		0.71 (0.31–1.65)	0.43

Conclusion

With this article, we present the preliminary results from the GRACE-M project, a multidisciplinary pathway based on the assessment of frailty and nutritional status in candidates for RC. Our findings support the adoption of a similar protocol for these patients and offer valuable insights for further exploring their management and the development of dedicated care pathways. Further studies should also investigate how to better predict RC outcomes using preoperative measures of functional and nutritional status.

Abbreviations

BMI, Body Mass Index; CCI, Charlson Comorbidity Index; ERAS, Enhanced Recovery After Surgery; FLIGS-FQ, the Functional Limitation and Geriatric Syndromes Frailty Questionnaire; CD, Clavien-Dindo; GRACE-M, Global Radical Cystectomy Evaluation and Management; MIBC, muscle-invasive bladder cancer; NMIBC, non muscle-invasive bladder cancer; NSQIP,

National surgical quality improvement project; RC, Radical Cystectomy.

Ethical approval and consent to participate

Ethical approval was obtained from the independent ethics committee of the IRCCS Humanitas Research Hospital (N 3317; 18/11/2022).

Conflicts of Interest

The authors declare not having any conflicts of interest.

Authors' contributions

PB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing- original draft, review and editing. CS: Formal analysis, Investigation,

Methodology, Validation, Visualization, Writing- review and editing. BB, FP, MP, SB, MVF and FS: Investigation, Methodology, Validation, Visualization, Writing- review and editing. RC, GL, NB and ML: Methodology, Validation, Visualization, Supervision, Writing- review and editing. AS and PC: Validation, Visualization, Supervision, Writing- review and editing. RH: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing- review and editing.

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