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Dipartimento di Medicina – DIMED
Direttore: Prof. Ch.mo *Paolo Simioni*
U.O.C. Anestesiologia e Terapia Intensiva
Direttore: Ch.mo Prof. *Paolo Navalesi*

Tesi di Laurea

Multimodal prehabilitation in patients requiring radical cystectomy: the impact of haemoglobin on outcomes.

Relatore
Dott.ssa Annalisa Boscolo Bozza

Correlatore
Dott. Enrique Moret

Laureanda
Gloria Gnan

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SUMMARY

Ø Abbreviations

6MWT: 6-minute walking test
BDI: Beck's depression inventory
BMI: body mass index
CEI: Comité de Ética de la Investigació
CFS: Clinical Frailty Scale
ERAS: Enhanced recovery after surgery
ESPEN: European Society for Clinical Nutrition and Metabolism
FP: frail patients
Hb: hemoglobin
HUGTiP: Hospital Universitario Germans Trias i Pujol
ICO: Istitut Català d'Oncologia
IPAQ-E-SF: International Physical Activity Questionnaire – Elderly – Short Form
MIP: maximal inspiratory pressure
MNA-SF: Mini Nutrition Assessment – Short Form
MP: multimodal prehabilitation
MUST: Malnutrition Universal Screening Tool
PFP: pre-frail patient
PreHAB: prehabilitation
PSQI: Pittsburgh sleep quality index
RPE (Borg scale): rating of perceived exertion
SPPB: short physical performance battery
WHO: World Health Organization

1 Abstract

1.1 Background

The ERAS (Enhanced Recovery After Surgery) protocol for abdominal surgery optimizes perioperative management in patients undergoing major surgery, improving prognosis and reducing hospital stay. Literature is now emerging in the field of prehabilitation, and the data we have so far suggest a positive influence on surgical outcomes, while anemia is one of the main risk factors for postoperative morbidity and mortality, and it is recommended that preoperative hemoglobin (Hb) levels be greater than 13g/dL, regardless of gender.
Bladder cancer (BC) is the fifth most frequent cancer in Italy. Most of the patients scheduled for radical cystectomy (RC) due to this cancer are smokers, anaemic, have a poor preoperative functional capacity and are at risk of malnutrition. Up to 65% of them present moderate to severe postoperative complications.

1.2 Aims of the study

The primary aim of this pilot study was to evaluate the impact of a multimodal prehabilitation (MP) program on hemoglobin levels and postoperative outcomes in patients undergoing radical cystectomy for bladder cancer. Specifically, the study sought to compare Hb levels between patients who underwent prehabilitation and a control group without prehabilitation, analyzing four distinct timepoints: t0, which is the time of diagnosis; t1, that coincides, in the cases, with the start of prehabilitation, and in the controls, with the end of chemotherapy; t2 that is the surgery date; and the discharge date is t3. Additionally, we aimed to examine the difference in Hb trends within the prehabilitation group, distinguishing between patients with baseline(t0) Hb <13 g/dL (G1) and those with Hb >13 g/dL (G2). The third objective was to assess whether there were significant differences in postoperative complication rates between G1 and G2.

1.3 Materials and methods

It is an observational, retrospective, uni-centre study held at the Germans Trias i Pujol Hospital. After ethics committee approval and signed informed consent by all participants, from November 2023 to May 2024, patients meeting inclusion criteria scheduled for radical cystectomy were preoperatively optimised during 4 weeks. The MP was conducted by our multidisciplinary team: anaesthesiologist, nurse, dietician, physiatrist, physiotherapist, psychologist. MP consisted in personalised physical training, nutritional and psychological support, anaemia correction (if Hb <13 g/dL) and cessation of smoking and drinking. The following variables were recorded: demographics, haemoglobin levels, anaemia, intraoperative blood loss, transfusion rates, functional capacity and frailty (through the 6 minute-walk-test, handgrip strength, Short Performance Physical Battery (SPPB), maximal inspiratory pressure, International Physical Activity Questionnaire (IPAQ), nutrition status (BMI, albumin, bioimpedance), anxiety/depression levels, length of stay and postoperative complications. Variables were recorded at 4 different times: t0, t1, t2 and t3.

1.4 Results

A total of 23 patients were included: 16 men and 7 women aged an average of 71,5 years old. Mean Hb level at t0 was 12,89 g/dL in the case group and 12,64 g/dL in the control group. A 69,6% of the case population was anaemic. A total of 16 cases received iron iv while 21,7% were assessed as frail. In the case population, the mean Hb level at t1 was 11,38 g/dL and still 69,9% of the population was still anaemic. In the control population the mean t1 Hb level was 11,26 g/dL.

Both at t0 and t1, there were no significant differences in Hb levels between the prehabilitation and control groups. However, by the time of surgery (t2), patients who underwent prehabilitation maintained higher Hb levels (mean 12.1 g/dL) compared to the control group (11.42 g/dL; p = 0.045). At discharge (t3), the difference remained significant (10.43 g/dL vs. 9.54 g/dL; p = 0.042). Within the prehabilitation group, G2 consistently demonstrated better Hb preservation, with mean levels of 13.71 g/dL at discharge (t3) compared to 11.22 g/dL in G1 (p = 0.044).

Finally, postoperative complications occurred more frequently in G1 than in G2, with rates of 83.33% versus 16.67%, respectively. Nevertheless, there were no statistically significant differences between groups in term of major complications (i.e. urinary tract infection, paralytic ileus, delirium, hemorrhage, acute kidney injury).

1.5 Conclusions

Prehabilitation can help maintain higher Hb levels at critical timepoints, such as the day of surgery and discharge, which is essential for reducing the risk of perioperative anemia and potential postoperative complications. Maintaining adequate Hb levels during the perioperative period is crucial, as anemia is known to compromise tissue oxygenation, impair wound healing, and increase the risk of infections and cardiovascular events.

The observed differences in Hb trends between patients with lower and higher baseline (t0) Hb levels (G1 <13g/dL and G2 >13g/dL) suggest that prehabilitation may be more beneficial for patients who enter surgery with higher initial Hb levels. This finding underscores the importance of individualized prehabilitation programs that take into account baseline hematologic status and provide targeted interventions for patients at higher risk of perioperative anemia.

Although the study did not show statistically significant differences in postoperative complication rates between G1 and G2, despite the trend toward fewer complications in G2 is clinically relevant. However, the lack of statistical significance in this area is likely due to the small sample size of the study, which limits the power to detect meaningful differences in complication rates. Future research should focus on larger, multicenter trials to confirm these findings and explore the long-term benefits of prehabilitation on surgical outcomes.

2 Riassunto

2.1 Introduzione

Il protocollo ERAS (Enhanced Recovery After Surgery) per la chirurgia addominale ottimizza la gestione perioperatoria nei pazienti sottoposti a chirurgia maggiore, migliorando la prognosi e riducendo la degenza ospedaliera. L'anemia è uno dei principali fattori di rischio per morbilità e mortalità postoperatorie: si raccomanda che i livelli di emoglobina (Hb) preoperatoria siano superiori a 13 g/dL, indipendentemente dal sesso.
Il cancro alla vescica è il quinto tumore più frequente in Italia. La maggior parte dei pazienti programmati per cistectomia radicale sono fumatori, anemici, hanno una scarsa capacità funzionale e sono a rischio di malnutrizione. Fino al 65% di questi pazienti presenta complicazioni postoperatorie moderate o gravi.

2.2 Obiettivi dello studio

L'obiettivo primario di questo studio pilota è valutare l'impatto di un programma di preabilitazione multimodale (PM) sui livelli di emoglobina e sugli esiti postoperatori in pazienti sottoposti a cistectomia radicale per cancro alla vescica. In particolare, lo studio mira a confrontare i livelli di Hb tra i pazienti sottoposti a preabilitazione e un gruppo di controllo, analizzando quattro timepoints distinti: t0, che corrisponde al momento della diagnosi; t1, che coincide, nei casi, con l'inizio della preabilitazione e nei controlli con la fine della chemioterapia; t2 è la data dell'intervento chirurgico; t3 è la data di dimissione. Si è esaminata, inoltre, la differenza nelle tendenze dell'Hb all'interno del gruppo di preabilitazione, distinguendo i pazienti con Hb basale (t0) <13 g/dL (G1) da quelli con Hb t0 >13 g/dL (G2). Il terzo obiettivo è valutare se vi sono differenze significative nei tassi di complicanzioni postoperatorie tra G1 e G2.

2.3 Materiali e metodi

Si tratta di uno studio osservazionale, retrospettivo e monocentrico, condotto presso l'Ospedale Germans Trias i Pujol di Badalona (Barcellona, Spagna). Dopo l'approvazione del comitato etico, da novembre 2023 a maggio 2024 i pazienti che hanno soddisfatto i criteri di inclusione e che erano in lista per cistectomia radicale sono stati ottimizzati preoperatoriamente durante 4 settimane. La PM è stata condotta da un *team* multidisciplinare: anestesista, infermiere, dietista, fisiatra, fisioterapista, psicologo. La PM consiste in un allenamento fisico personalizzato, supporto nutrizionale e psicologico, correzione dell'anemia (se Hb <13 g/dL) e cessazione del fumo e del consumo di alcol. Sono state registrate le seguenti variabili: dati demografici, livelli di emoglobina, anemia, perdita di sangue intraoperatoria, tassi di trasfusione, capacità funzionale e fragilità (attraverso il *6 minute walking test*, *grip strength*, *Short Physical Performance Battery* (SPPB), pressione inspiratoria massima, questionario sull'attività fisica *"International Physical Activity Questionnaire"* (IPAQ), stato nutrizionale (BMI, albumina, bioimpedenza), livelli di ansia/depressione, durata della degenza e complicanze postoperatorie. Le variabili sono state registrate in 4 momenti diversi: t0, t1, t2 e t3.

2.4 Risultati

Un totale di 23 pazienti è stato arruolato: 16 uomini e 7 donne con un'età media di 71,5 anni. Il livello medio di Hb a t0 era di 12,89 g/dL nel gruppo dei casi e di 12,64 g/dL nel gruppo di controllo. Il 69,6% della popolazione dei casi era anemica. Un totale di 16 pazienti ha ricevuto ferro per via endovenosa, mentre il 21,7% è stato classificato come fragile. Nel gruppo dei casi, il livello medio di Hb a t1 era di 11,38 g/dL e il 69,9% della popolazione era ancora anemica. Nel gruppo di controllo, il livello medio di Hb a t1 era di 11,26 g/dL. Sia a t0 che a t1, non c'erano differenze significative nei livelli di Hb tra i gruppi di preabilitazione e di controllo. Tuttavia, al momento dell'intervento chirurgico (t2), i pazienti sottoposti a preabilitazione hanno mantenuto livelli di Hb più elevati (media 12,1 g/dL) rispetto al gruppo di controllo (11,42 g/dL; $p = 0,045$). Alla dimissione (t3), la differenza è rimasta significativa (10,43 g/dL contro 9,54 g/dL; $p = 0,042$). All'interno del gruppo di preabilitazione, G2 ha costantemente dimostrato una migliore conservazione dell'Hb, con livelli medi di 13,71 g/dL alla dimissione (t3) rispetto a 11,22 g/dL in G1 ($p = 0,044$). Infine, le complicanze postoperatorie si sono verificate più frequentemente in G1 rispetto a G2, con tassi del 83,33% rispetto al 16,67% sul totale. Non vi erano differenze statisticamente significative tra i gruppi in termini di complicanze maggiori (ad es. infezione urinaria, ileo paralitico, delirio, emorragia, insufficienza renale acuta).

2.5 Conclusioni

La preabilitazione si è dimostrata utile nel mantenere i livelli di emoglobina più elevati in momenti cruciali come il giorno dell'intervento e la dimissione, riducendo così il rischio di anemia perioperatoria e delle relative complicanze postoperatorie. Mantenere livelli adeguati di Hb nel periodo perioperatorio è fondamentale, poiché l'anemia è nota per compromettere l'ossigenazione dei tessuti, rallentare la guarigione delle ferite e aumentare il rischio di infezioni e complicazioni cardiovascolari.
Le differenze osservate nelle tendenze dell'Hb tra i pazienti con livelli basali di Hb insufficienti (<13 g/dL) e quelli con livelli buoni (>13 g/dL) indicano che la preabilitazione potrebbe essere particolarmente vantaggiosa per coloro che entrano in sala operatoria con livelli di Hb più elevati. Questo risultato sottolinea l'importanza di personalizzare i programmi di preabilitazione, tenendo conto dello stato emoglobinico di ciascun paziente, e fornire interventi mirati ai soggetti maggiormente a rischio di anemia perioperatoria.
Nonostante lo studio non abbia mostrato differenze statisticamente significative nei tassi di complicanze postoperatorie tra i due gruppi, la tendenza verso un minor numero di complicanze nel gruppo con Hb più elevata (G2) è clinicamente rilevante. Tuttavia, la mancanza di significatività statistica potrebbe essere legata alla piccola dimensione del campione, che limita la capacità di rilevare differenze significative. Studi futuri, con campioni più ampi e condotti su scala multicentrica, saranno necessari per confermare questi risultati e approfondire i benefici a lungo termine della preabilitazione sugli esiti chirurgici.

3 Introduction

3.1 Bladder cancer

Bladder cancer (BC) is the ninth most common cancer worldwide[1] and the fifth most common in Europe and Italy[2].
It appears typically with hematuria, which can lead to anemia, and storage lower urinary tract symptoms, while the remainder of cases are asymptomatic or incidental findings.

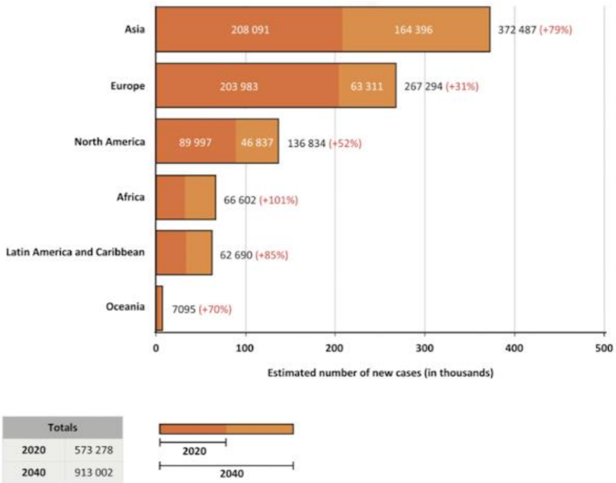

Figure 1- Estimated number of new bladder cancer cases between 2020 and 2040 (both sexes). Adapted from the Global Cancer Observatory: cancer tool by IARC.

Regarding etiology, the theory that there is a synergistic effect between an individual's genetic predisposition and exposure to risk factors is once again adopted. The International Agency for Research on Cancer (IARC) has reported sufficient evidence for the following risk factors:

- tobacco smoking: nearly 50% of BC cases are caused by it[3]. The aromatic amines and polycyclic aromatic hydrocarbons within the tobacco smoke, which undergo renal excretion, are linked to the development of BC. The risk is directly proportional to smoking intensity up to 20 cigarettes per day, but plateaus thereafter. In contrast, BC risk increases without plateau with smoking duration. The risk decreases with time since smoking cessation;
- various occupational exposures (aluminum production, rubber production, painting, firefighting, occupational exposure to various dyes or dye intermediates);
- environmental exposures (X radiation or gamma radiation, and arsenic);
- medications (cyclophosphamide and chlornaphazine);
- opium consumption;
- Schistosoma infection.

Most BC cases are urothelial carcinoma (UC), including squamous cell, sarcoma, lymphoma, and adenocarcinoma, and approximately 75% of these are non–muscle-invasive BC (NMIBC)[4]. When the disease has not progressed to a deeper level, surpassing the mucosa and the basement membrane, it can be treated with conservative methods that can be summarized as follows:

- transurethral resection of the mass
- intravesical immunotherapy
- systemic chemotherapy

NMIBC has a high prevalence due to its indolent natural history and high recurrence rate.

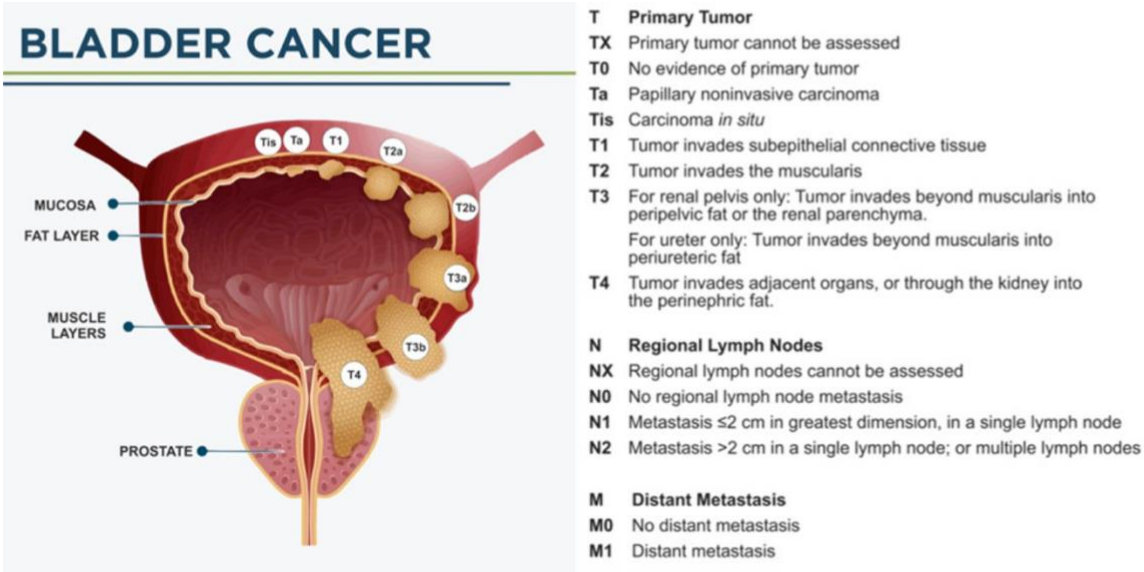

Figure 2 - Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J. Dec 2009;3(6 Suppl 4):S193-8.

On the other hand, around one-quarter of BC cases are muscle invasive (T2 or more at the TNM staging). The guidelines provide the following treatment options:

- the association of systemic chemotherapy and immunotherapy;
- a radical surgical treatment named radical cystectomy with urinary diversion;
- palliation is the only approach we have if the tumor is already metastatic.

Generally, the prognosis for patients with invasive, progressive, or metastatic bladder cancer is poor. The prognosis for patients with bladder squamous cell carcinoma is also unfavorable, as these tumors are typically highly infiltrative and often diagnosed at an advanced stage[5].

The treatment landscape for BC is burdensome, protracted, and expensive. It is known to impose a significant burden on the healthcare system in Europe[3], not only due to its incidence rate but especially because of the costs associated with treatments, lifelong follow-ups, and measures adopted for patient comfort. In fact, the highest risk for pain, constipation, and poor quality of life has been observed in patients with bladder cancer compared to all other cancer sites[6]. Bladder cancer represents the most expensive malignancy in the United States and Central Europe[7].

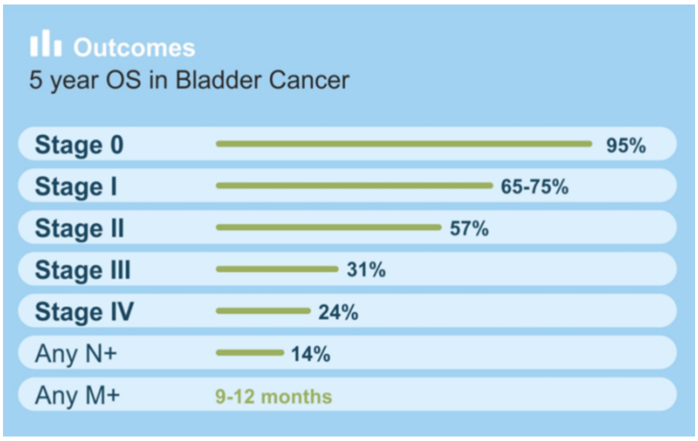

Figure 3 - Bladder cancer 5-year survival and mortality rates of stage-specific bladder cancer in the United States: a trend analysis. Cancer Epidemiol. Jun 2013;37(3):219-25.

Patients with BC are often described as frail and can experience concurrent other frequent and urgent medical conditions, and as part of a heavy comorbid burden, they require particular attention during evaluation before scheduled surgery[8]. Candidates for RC for MIBC or high-risk NMIB constitute a group of patients with high perioperative risk in the short-term and significantly reduced physical and psychological health in the longer-term. Patients can be described as people around 70 years of age, with a high comorbidity index, and approximately 27% are at severe nutritional risk and 30% are current smokers. Overall, patients undergoing RC are a frail population with a high risk of perioperative morbidity. Evidence has identified that patients undergoing RC can experience complications rates between 64% and 90% within the first 3 months postoperatively[9]. In combination with advanced age, the effects of malignancies can be even more devastating since elderly patients often already have reduced physiological reserves, and comorbidities can limit treatment options and promote complications, thereby leading to greater impairment during the process of recovery.

In relation to that and to the organization of the BC pathway, there is growing evidence of prehabilitation, which has caused an emerging paradigm-shift in surgical cancer care, and an essential integrated component of the cancer care continuum. Unfortunately, systematic screening for lifestyle factors, frailty or follow-up aiming at risk reducing still lack awareness and may be because of a lack of understanding the potential benefit of the prehabilitation approach. The potential of multimodal prehabilitation and how it can be easily integrated in the BC pathway at any stage is now being studied and will probably be a gold standard in the future years: there is emergent interest in moving forward to it.

3.2 Radical cystectomy

Radical cystectomy is the gold standard treatment for MIBC and high-grade NMIBC. It consists in a surgical procedure in which the entire bladder and regional lymph nodes are removed. In men, the prostate gland and seminal vesicles are also typically removed, while in women, the uterus, fallopian tubes, ovaries, and the anterior part of the vagina are excised. It can be performed either through laparotomy or laparoscopy. Naturally, the open surgery is a more invasive and less tolerated approach: an incision is made vertically from the umbilical region to the pubis, through which the affected organs are extracted. Despite advances in technology and patient care, open RC still has high rates of perioperative complication and mortality even in the most experienced hands at high volume centres[10].
There have been numerous studies analyzing if robot-assisted RC (RARC) can improve outcomes of this highly morbid surgery: trials showed decreased blood loss and increased length of surgery, but the length of stay and pathology outcomes were similar and RARC was significantly less cost effective[11].

3.2.1 Urinary diversion

Urinary diversion is a surgical method to create a new way to pass urine out of the body after the bladder has been removed and therefore a necessary component of RC. Two general categories of diversion can be distinguished: incontinent and continent diversion.

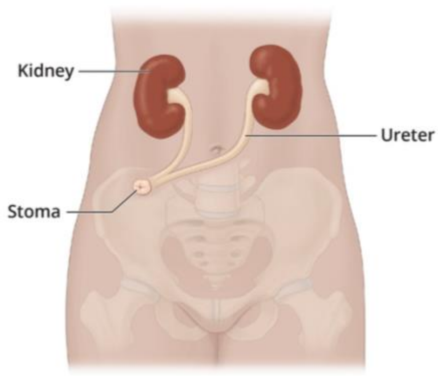

Figure 4 - Cutaneous ureterostomy.

Incontinent diversions are more widely used as they are technically easier to perform and are more easily managed by the elderly, frail population[12]. The simplest diversion is the cutaneous ureterostomy (Figure 4), which, however, fell out of favor due to the high risk of stricture of the ostomy sites. The advantage of this strategy is the avoidance of a bowel anastomosis, which reduces the risk of complications, especially in patients who may otherwise be marginal for RC.

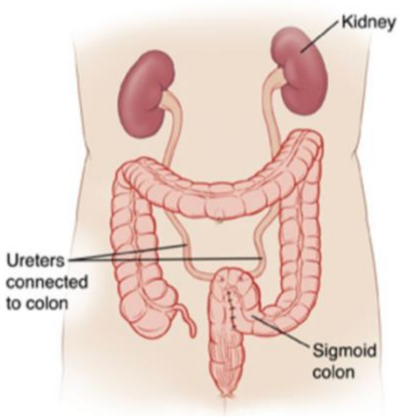

Figure 5 - Ureterosigmoidostomy.

Similarly, the ureterosigmoidostomy (Figure 5) was a simple method for urinary diversion, but it too has fallen out of favor due to the risk of pyelonephritis and adenocarcinoma at the site of ureteral implantation into the colon[13].
Ileal conduits (Figure 6) were the benchmark for urinary diversion before continent diversions were described and remain the procedure of choice especially in older patients and patients with significant other comorbidities.

The continent diversion is further divided into continent cutaneous diversion and orthotopic neobladder. Patients with a continent cutaneous diversion are committed to lifelong intermittent self-catheterization. With reported daytime and nighttime continence rates of 90% to 98%, this method of reconstruction is associated with a good quality of life post RC in most patients[14]. This technique is less frequently used with the advent of the orthotopic urinary diversion.

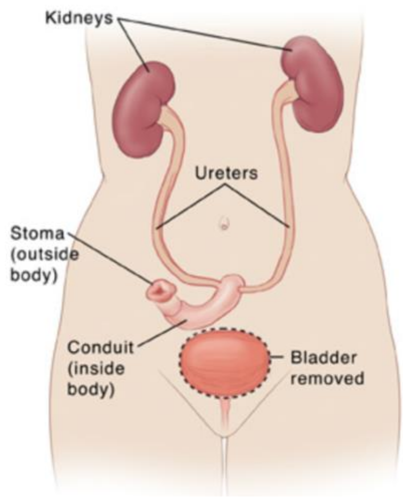

Figure 6 – Bricker ileal conduit.

Voiding of the orthotopic neobladder is accomplished via relaxation of the external sphincter combined with the Valsalva maneuver. Daytime continence rates exceed 85% at high volume centers but do vary between 47% to 100% depending on the definition of continence and the length of follow-up[15]. Up to 50% of patients have nocturnal incontinence due to loss of physiological storage reflexes. Higher rates of ventral hernias may be observed after neobladder construction due to the use of Valsalva voiding. Intermittent self-catheterization after neobladder surgery is required due to incomplete bladder emptying in approximately 4% to 25% of patients based on a meta-analysis of more than 2,000 patients and is significantly more predominant in women[16].

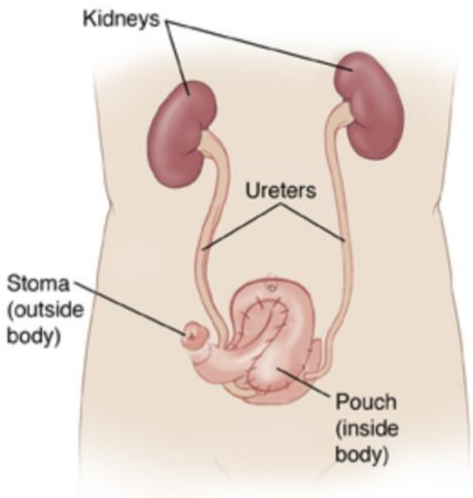

Figure 7 - Continent urinary diversion: cutaneous diversion.

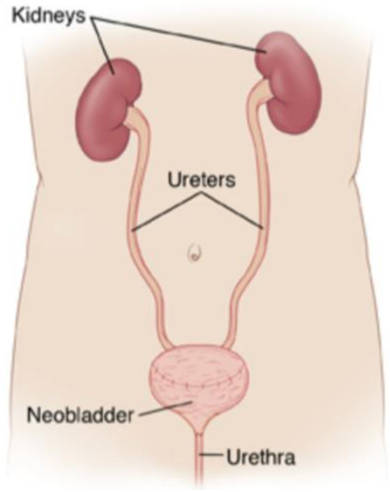

Figure 8 - Continent urinary diversion: orthotopic neobladder.

3.2.2 Complications

RC is associated with relatively high perioperative morbidity and mortality, despite improvements in surgical techniques and peri-operative care. The incidence of complications after surgery has been reported to be in the range of 30–70%[17].

Complications related to RC can be divided into early and late, with early complications referring to those that occur within 30 days of the operation and late encompassing complications occurring between 30–90 days. Postoperative mortality rates range from 0.8% to up to 3%[17].

Reported common late complications include ventral hernia (17%), calculus formation (16%), ureteroenteric strictures (14%) and parastomal hernias (8%).

Shabsigh and colleagues in 2009 provided one of the first systematic reports of post RC complications using the standardized Clavien-Dindo classification. They analyzed data from 1,142 consecutive cystectomies between 1995 and 2005 and found that 735 (64%) experienced a complication within 90 days of surgery. The majority of these (79%) were grade 1 to 2 and considered to be “minor”. Most patients (58%) had one or more complication within the first 30 days after surgery[18].

The most common complication categories were gastrointestinal (29%), infectious (25%), wound-related (15%), cardiac (11%), and genitourinary (11%); however, this pattern did change from early to the late phase of complications. The most common early all-grade complications were gastrointestinal, infectious and wound-related. This switched to infectious, gastrointestinal and genitourinary in the late phase. It must be noted, however, that in both early and late phase, the most common high-grade complications were genitourinary[18].

An important advance in our efforts to reduce perioperative complications and improve post-operative quality of life has been the implementation of Enhanced Recovery after Surgery (ERAS) pathways that define numerous evidence-based standard interventions to be followed from pre-operative education and optimization to intra-operative fluid and analgesia management and post-operative early nutrition and mobilization[19]. Although the impact of any one element is often uncertain, there is compelling evidence that the cumulation of elements shortens hospitals stays and reduces the rate of complications[10].

The negative impact on quality of life and the high rate of peri-operative complications poses important limitations, especially in the context of a disease that affects primarily elderly patients with multiple medical co-morbidities and frailty.

3.3 Perioperative protocol: ERAS items

Currently, perioperative management for major surgeries is based on the Enhanced Recovery After Surgery (ERAS) protocol, which follows a multimodal approach. The ERAS protocol is a comprehensive pathway aimed at reducing surgical stress and maintaining bodily homeostasis to enable a rapid postoperative recovery for patients undergoing major surgery. The core principles of the ERAS protocol focus on:

- optimal pain control through a combined approach;
- minimally invasive surgical techniques;
- preoperative counseling and early postoperative rehabilitation.

The objectives include optimizing perioperative care by using evidence-based practices, promoting better recovery of patient autonomy after surgery, reducing hospital stay durations, lowering the incidence of complications, minimizing hospital readmissions, and reducing costs.

The ERAS Society – Urology Chapter was officially formed at the 2016 World Congress in Lisbon. The group was chaired be Yannick Cerantola until 2018 and is now chaired by Dr Sia Daneshmand. The adoption by urologists of ERAS protocols has dramatically improved the perioperative care of patients undergoing RC[11]. These protocols include preoperative, intraoperative, and postoperative modifications to enhance recovery and reduce stress following surgery. In 2013, the ERAS Society published guidelines for perioperative care after radical cystectomy. Since the publication of these guidelines and initial implementation of ERAS protocols, evidence supporting the use of ERAS after radical cystectomy has grown: reduction of low grade complications (Clavien-Dindo classification <2), reduced postoperative hospital stay, reduction in the time to first bowel movement and reduced intensity of pain[10].

In Italy, the ERAS (Enhanced Recovery After Surgery) program began to be gradually adopted in the mid-2010s, driven by increasing scientific evidence of its benefits and the interest of hospitals and healthcare professionals in improving postoperative outcomes. Key milestones include the period from 2013 to 2015, when several Italian hospitals started experimenting with ERAS protocols, often in pilot projects for specific surgeries such as colorectal surgery. In 2016, the ERAS Italy Association was founded to promote and coordinate the implementation of ERAS protocols across the country, playing a crucial role in training healthcare professionals and spreading awareness. By 2017, numerous conferences and workshops further raised awareness of ERAS's benefits, leading many hospitals to formally adopt the protocols. From 2018 onwards, the program's implementation became more widespread, with many hospitals adopting ERAS protocols in various surgical departments. The ERAS Italy Association continues to support hospitals with training and standardization efforts, aided by international collaborations and participation in European networks focused on surgical quality improvement.

The ERAS protocol consists of many evidence-based items aimed at maintaining the homeostasis of the surgical patient, both on a physical and a psychological level, and reducing the profound stress response following the surgery. These measures are set up in the different timings, covering the whole perioperative process.

3.3.1 Preoperative care

The preoperative patient's management consists in:

Preadmission counselling and patient family education
Studies have shown that reducing anxiety by providing detailed information about admission, surgical, and anesthetic procedures can improve pain control[20], early mobilization, and perioperative feeding, thereby reducing postoperative complications[21].
Before the first ERAS studies in urology, a 2000 report found that 65-71% of patients scheduled for various types of urinary diversion had not received information about their therapy options before being admitted to the Department of Urology[22].

Over the past two decades, the significance of preadmission counseling and patient education, coupled with a comprehensive explanation of the perioperative pathway, has grown substantially. Although specific studies exclusively focusing on preadmission counseling and education are lacking, these elements have been examined within the broader context of ERAS protocols.
Dutton et al. conducted a study involving 165 patients undergoing open radical cystectomy with urinary diversion under the ERAS protocol. The study detailed a tripartite approach to patient education and counseling: initial pre-referral guidance by their family doctor, outpatient evaluations by nurse specialists, and thorough preoperative education sessions explaining ERAS protocols and stoma or neobladder care prior to hospital admission. The authors underscored the importance of informing patients at the earliest possible stage. The study concluded that implementing ERAS components was safe, supporting early patient feeding, early mobilization, and expedited hospital discharge[23].

Tobacco smoke and alcohol cessation

Cigarette smoking is associated with increased risks of pulmonary and cardiovascular diseases, as well as heightened postoperative morbidity and mortality. Discontinuing smoking in the weeks preceding surgery can mitigate these risks[24]. Surgeons and anesthesiologists should assess patients' smoking habits prior to scheduled operations to offer suitable smoking cessation education and resources. A combined approach of nicotine replacement therapy, pharmacotherapy, and counseling has been shown to be effective in achieving long-term smoking cessation[24]. Surgical patients who attempt to quit smoking during the preoperative period exhibit significantly higher cessation rates compared to the general population, indicating that the time surrounding surgery is an optimal period for encouraging and maintaining behavior change.
Almost 80% of radical cystectomy patients are current or former smokers[25]. Preoperative smoking cessation can potentially reduce the risk of pneumonia, prolonged mechanical ventilation beyond 48 hours, and unplanned tracheal intubation. Active smokers have higher incidences of myocardial infarction, postoperative cardiac arrest, stroke, deep vein thrombosis, and sepsis. A systematic review of urological and genitourinary patients indicated that intensive smoking cessation interventions, including individual counseling and pharmacotherapy one or two months before surgery, lowered the risk of postoperative complications[26]: ERAS guidelines for urology recommend smoking cessation 4–8 weeks before surgery.
Furthermore, consuming more than two to three alcoholic drinks daily diminishes the immune response, prolongs bleeding time, and heightens the endocrine stress response to surgery[27]. However, a 4-weeks preoperative abstinence from alcohol significantly reduces the exaggerated surgical stress response in alcohol abusers[27].

Nutritional screening

It is widely recognized that inadequate nutrition negatively affects postoperative outcomes[28]. This issue often accompanies comorbidities and diseases like cancer: up to 33% of urology patients undergoing surgery are at nutritional risk[11]. For cancer patients undergoing surgery, poor nutrition is an independent risk factor for complications, extended hospital stays, and increased costs[29]. The significance of nutritional status in patients undergoing radical cystectomy has been acknowledged for some time, with complication rates reported as high as 80% in malnourished patients[30]. Recent data from Vanderbilt University show that preoperative nutritional deficiencies are strong predictors of 90-day mortality and poor overall survival[31]. Regarding the definition of the problem, the European Society of Parenteral and Enteral Nutrition (ESPEN) identifies "severe" nutritional risk as meeting one or more of the following criteria:

- a weight loss of more than 10% to 15% within 6 months;
- a body mass index (BMI) below 18.5 kg/m²;
- serum albumin levels under 30 g/L.

Similarly, the British Association of Parenteral and Enteral Nutrition employs these parameters in the Malnutrition Universal Screening Tool (MUST) to stratify patients based on their nutritional status. It is particularly noteworthy that many patients undergoing radical cystectomy would be classified as high risk or at severe nutritional risk after a proper assessment. Addressing preoperative nutritional deficiencies may sometimes necessitate extended parenteral nutrition or a combination of parenteral and enteral nutrition, depending on the severity of the deficiency and the patient's gastrointestinal function.

Minimal fasting and fluid and carbohydrate loading

The ERAS program aims to limit the body’s catabolic response to surgery. Autonomic afferent signals from the injury site stimulate the hypothalamus-pituitary-adrenal axis, triggering the body’s endocrine response[32]. Increased cortisol levels drive gluconeogenesis and glycogenolysis in the liver, converting triglycerides into glycerol and fatty acids, which serve as substrates for gluconeogenesis. The production of adrenocorticotropic hormone and cortisol leads to protein catabolism, resulting in weight loss, muscle wasting (both skeletal and visceral), and nitrogen loss. Additionally, a relative insulin deficiency and peripheral insulin resistance occur due to alpha-2-adrenergic inhibition of pancreatic beta cells (facilitated by catecholamines) and defects in the insulin receptor/intracellular signaling pathway. Consequently, hyperglycemia is a significant finding after cystectomy[33], and insulin resistance is a major factor influencing length of stay, poor wound healing, and increased risk of infections[34]. The extent of insulin resistance is correlated with the surgical magnitude, and controlling postoperative hyperglycemia can reduce mortality and morbidity by half[35]. Strategies to reduce insulin resistance include adequate pain management, avoiding prolonged interruptions in oral intake, and carbohydrate loading.

Preoperative administration of enteral formulas with high quality protein foods (for around two weeks) and immunonutrients (for five days before surgery) reduces the rate of postoperative complications by up to one third and the risk of infectious complications by up to 40%[36].

Hydration needs special attention in old patients since they have a diminished sensation of thirst and preoperative dehydration has been associated with increased postoperative morbidity. This is part of the Enhanced Recovery After Surgery (ERAS) protocol, as is carbohydrate loading with 800 ml in the evening and 400 ml 2-3 hours before surgery[11].

Traditionally, patients are fasted from midnight to prevent pulmonary aspiration after elective surgery, although no evidence supports this practice. Preoperative fasting actually exacerbates metabolic stress, hyperglycemia, and insulin resistance, which are already heightened during surgery[34]. Avoiding preoperative fasting decreases insulin resistance, protein loss, and improves muscle function[37]. Allowing patients to consume solids up to six hours before surgery and clear fluids up to two hours before does not increase complications;

moreover, carbohydrate loading helps attenuate postoperative insulin resistance, reduces nitrogen and protein losses, preserves skeletal muscle mass, and alleviates preoperative thirst, hunger, and anxiety[38]. These metabolic benefits also promote faster recovery through early return of bowel function and shorter hospital stays, enhancing perioperative well-being[39]. Therefore, the European Society of Anesthesiology fasting guidelines advise patients to consume clear liquids, such as tea, coffee without milk, and water, up to two hours before elective surgery. They recommend, with the highest level of evidence, that solid food intake be prohibited six hours before elective surgery.
In major urologic surgery, Rege et al. reduced the preoperative fasting period by allowing clear liquids up to two hours before laparoscopic live kidney donor surgery in ERAS patients[40]. They noted that shortening the preoperative fasting period improved patient comfort, reduced thirst and anxiety, and facilitated faster recovery. Their study showed that patients following the ERAS perioperative pathway had shorter hospital stays. Conversely, some early fast-track studies of patients undergoing laparoscopic radical prostatectomy allowed liquid intake only until midnight on the preoperative day. Even without this preoperative ERAS component, the authors observed shorter hospital stays in the ERAS group.

No or limited bowel preparation

The routine use of preoperative mechanical bowel preparation (MBP) has been a long-standing practice in colorectal surgery and is commonly applied to patients undergoing radical cystectomy due to the involvement of bowel segments. MBP aims to clear the large intestine of solid fecal matter and reduce the bacterial load, thereby decreasing the risk of postoperative complications. However, MBP liquefies solid feces, potentially increasing the risk of intraoperative contamination. Moreover, it is nearly impossible to significantly reduce the bacterial load in the bowel because of the vast number of microorganisms present in the digestive tract[41]. MBP can cause metabolic and electrolyte imbalances, dehydration, abdominal pain, bloating, and fatigue[42], and may even negatively impact surgical outcomes[43].

Antimicrobial prophylaxis

The European Association of Urology guidelines[44] suggest the optional use of antimicrobial prophylaxis for RC and nephrectomy due to the lack of studies on this subject. For RC patients, prophylaxis against both aerobic and anaerobic pathogens is recommended. The recommended regimen includes a combination of cefuroxime, aminopenicillin/beta-lactamase inhibitor, and metronidazole. If the surgery is prolonged or significant morbidity factors are present, antimicrobial prophylaxis may be extended to less than 72 hours. However, prolonging antibiotic prophylaxis is not recommended if urinary drainage remains in place post-surgery.

Thromboprophylaxis

Patients undergoing radical cystectomy are at high risk for venous thromboembolism (VTE) due to the underlying cancer and the prolonged duration of the surgical procedure, which typically exceeds 120 minutes[45]. Novotny et al.[46]reported an approximately 5% incidence of clinically significant deep vein thrombosis in RC patients, while Vukina et al. observed an incidence of 1–5% in open RP and just 0.5% in robotic procedures.
European guidelines on perioperative VTE prophylaxis for fast-track surgery[45] recommend administering the first dose of low-molecular-weight heparin (LMWH) either 12 hours before

the procedure or 6–8 hours afterward. For patients undergoing planned neuraxial anesthesia, postoperative administration may be preferred. Additionally, use of graduated compression stockings or compressive stockings can enhance thromboprophylaxis efficacy.
The ERAS Society guidelines for rectal/pelvic surgery[47] recommend considering extended prophylaxis for four weeks in patients at increased risk of VTE, aligning with the American College of Chest Physicians guidelines[48], which also emphasize extended prophylaxis for high-risk cancer patients.

Optimization of medical conditions
Preoperative optimization involves assessment and improvement of medical conditions, as well as the reduction of risks that affect perioperative homeostasis. The guidelines provided by the European Society of Anesthesiology on preoperative evaluation[49] recommend different strategies that should be used for reducing perioperative risks.

Antiemetic prophylaxis
There is insufficient evidence regarding the incidence of postoperative nausea and vomiting (PONV) following urologic surgery. Nevertheless, PONV can exacerbate postoperative pain, wound dehiscence, and hematoma, thereby increasing patient distress[50]. To reduce the incidence of PONV, it is essential to assess the patient's baseline risk using validated scoring systems.
After determining baseline risk, PONV prevention should be addressed throughout all three phases of the ERAS pathway: preoperative, intraoperative, and postoperative. This is particularly important in laparoscopic urologic surgery. For instance, a non-randomized retrospective analysis of laparoscopic nephrectomy patients[51] implemented a regimen where antiemetics were initiated preoperatively with a scopolamine patch, dexamethasone and ondansetron were administered intraoperatively, and scopolamine and ondansetron were given postoperatively. Rescue antiemetics were also recommended for the preoperative and postoperative phases. Although the study did not specifically analyze PONV rates, the intervention group experienced reduced hospital stays.
In another prospective study of RC patients[52], guided intraoperative fluid therapy significantly reduced the incidence of PONV.

3.3.2 Intraoperative care

Analgesia
The use of neuraxial anesthesia in RC patients is widely recognized as a critical component of fast-track pathways. The American Pain Society emphasizes the importance of neuraxial anesthesia in major thoracic and abdominal surgeries, particularly for patients with cardiac and pulmonary comorbidities or those at risk of postoperative ileus.
Epidural anesthesia offers several benefits for the general perioperative status of patients: multiple studies have demonstrated that it can reduce mortality rates and lower the risk of cardiovascular and respiratory events in abdominal surgeries[53]. In RC patients, epidural anesthesia is associated with reduced intraoperative blood loss, earlier recovery of gastrointestinal peristalsis, and better postoperative pain control[54].
It is crucial to further investigate the use of epidural anesthesia in major urologic surgeries. The optimal level for epidural insertion in different urologic procedures has not been precisely

defined. However, the ERAS guidelines for RC strongly recommend using thoracic epidural anesthesia for 72 hours, based on extrapolated results from rectal surgery[11].
Alternative methods for administering perioperative analgesia in urology have shown promising results, such as rectus sheath catheter (RSC) analgesia. Authors have transitioned from regional anesthesia to RSC blocks due to their numerous benefits. Studies have highlighted the advantages of RSC blocks, including high placement success rates, patient safety, suitability for patients on antiplatelet medications, and reliability during postoperative care[55].

Fluid Therapy

The optimization of fluid therapy within fast-track pathways aims to achieve a 'zero balance,' maintaining preoperative fluid composition and weight. Gupta and Gan recommend that maintenance fluid therapy during major abdominal surgery for adult patients should be administered at 1–3 ml/kg/h[56].
A prospective study on intraoperative fluid therapy in RC[52], patients were randomized to receive either standard intraoperative fluid therapy or esophageal Doppler-guided fluid therapy. The study showed that the intervention group experienced improved gastrointestinal function, with significant reductions in ileus, PONV, and wound infections. These patients received significantly greater volumes of intravenous fluid during the first operative hour, which was suggested to prevent occult splanchnic hypoperfusion and lower postoperative complications. The authors emphasized that the timing of fluid administration might be more critical for tissue perfusion than the volume.
The controversy over fluid management in RC persists. Fluid restriction, which risks silent or evident splanchnic ischemia and hypotension, must be balanced against fluid overload, which can lead to interstitial and gut edema. There is a need for better monitoring of bowel perfusion and standardized intraoperative fluid administration protocols within ERAS pathways for RC and other major urologic procedures.

3.3.3 Postoperative care

Nutrition and nasogastric tube (NGT)

In addition to preoperative carbohydrate loading, early postoperative nutrition can improve the metabolic response leading to less insulin resistance, lower nitrogen losses and reduce the loss of muscle strength[57]. One of the early meta-analyses, although relatively small, found that there is no advantage in keeping patients nil by mouth after elective gastrointestinal resection and early feeding may actually be beneficial by reducing infectious complications and length of hospital stay[58]. Lewis and colleagues demonstrated no detrimental effect with early feeding, but a trend towards a lower incidence of anastomotic dehiscence, wound infection, pneumonia, intra-abdominal abscess or mortality in patients who received early enteral feeding[58].
Prophylactic nasogastric tubes placed during surgery to evacuate air, should be removed before reversal of anesthesia. Fever, oropharyngeal and pulmonary complications are more frequent in patients with nasogastric tubes[59]. Avoidance of nasogastric decompression is associated with an earlier return of bowel function[59] while gastroesophageal reflux is increased during laparotomy if nasogastric tubes are placed[60].

Removing the NGT on the first day and introducing clear liquid on the second post-operative day showed improvement in postoperative morbidity[61]. The combination of metoclopramide and early nasogastric suction removal in RC patients has been studied and it revealed reduction of postoperative atelectasis and earlier tolerance of solid food without complications regarding bowel anastomosis[62].

Analgesia

Epidural analgesia administered for 2–3 days post-surgery, preferably without opioids, has been shown to provide more effective pain relief compared to patient-controlled analgesia in colorectal surgery[63]. In the context of urologic surgery, a study by Hong et al. found that postoperative pain scores were lower in patients who received combined general and epidural anesthesia compared to those who had general anesthesia alone for radical prostatectomy[64]. The authors suggested that this approach might help reduce the incidence of postoperative chronic pelvic pain.

As previously mentioned, rectus sheath catheter analgesia for RC is gaining attention as alternatives to neuraxial anesthesia for perioperative analgesia. The combination of motor blocks with oral paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) could potentially eliminate the need for opioids in postoperative pain management[65].

Postoperative ileus

The postoperative ileus (POI) has been defined as the "inability to tolerate solid food by postoperative day five, the need to place a nasogastric tube, or the need to stop oral intake due to abdominal distension, nausea, or emesis."[18]. The POI is a common gastrointestinal complication, particularly after RC, with an incidence ranging from 4% to 31%[46]. Proposed mechanisms for POI after RC include fluid overload, electrolyte shifts, bowel manipulation, and opioid use.

Studies have shown that patients following an ERAS pathway experience a significant reduction in the average time to the first passage of stool compared to those in pre-ERAS groups[66]. The prevention of POI involves the cumulative benefits of various ERAS elements, including epidural perioperative analgesia, optimization of intraoperative fluid therapy, minimally invasive surgical approaches, early NGT removal with early oral intake, and early mobilization.

Additional measures to promote bowel function and prevent ileus include chewing gum and the use of alvimopan. In a study on robotic RC, patients who chewed gum had a shorter time to first flatus compared to those who did not[67]. A retrospective study by Hamilton et al. found that patients undergoing RC who received alvimopan had a significantly shorter average time to resume a regular diet[68].

Nutrition and early oral intake

Several studies have demonstrated the safety of early oral intake following bowel anastomosis[69],[70]. The guidelines for perioperative care in elective rectal/pelvic surgery recommend an "ad libitum" oral diet 4 hours after rectal surgery[47]. It has been found that improving postoperative care in RC patients by reducing the time to clear liquid and regular diet resulted in better outcomes[61] and it also leads to a reduction in total and postoperative

hospital stay[71]. Early oral nutrition, as part of a multimodal approach, was shown to reduce the time to first flatus.
The ESPEN guidelines for surgery recommend initiating oral intake, including clear liquids, within hours after surgery for most patients[72]. The ERAS society guidelines[11] for perioperative care after RC advocate for reestablishing a normal diet as soon as possible.
In cases where oral or enteral tolerance is impaired for more than seven days, ESPEN guidelines recommend the addition of parenteral nutrition. Early parenteral nutrition is beneficial for malnourished patients when oral or enteral nutrition is not feasible.

Early mobilization

Prolonged bed rest can lead to a range of detrimental effects, including respiratory, musculoskeletal, and neuropsychological changes[73]. To ensure successful patient mobilization post-surgery, key conditions must be met: patient motivation, effective postoperative pain relief, and the prevention of orthostatic intolerance. Implementing a structured mobility plan with active intervention from a physiotherapist leads to increased time out of bed and improved grip strength.
In the context of RC, early mobilization as part of the ERAS protocol has been shown to reduce both the length of hospital stay and the frequency of readmissions[74].

3.4 Geriatric considerations

According to the WHO, the world population aged 65 or older will grow from 500 million in 2010 to nearly 1.5 billion in 2050[75]. Given such a rapidly aging population, most BC patients will soon be over the age of 75, and their management will inevitably pose a serious challenge to healthcare systems[76]: in fact, older persons are characterized by high clinical complexity, with consequent polypharmacy, disabling conditions, and social issues

By the Charlson Comorbidity Index, (CCI) over 50% of BC survivors have a moderate to severe comorbidity burden, and BC patients a median of eight chronic conditions[77]. Even if there the presumption is willing to give the most effective treatment possible, since untreated BCs have a very poor prognosis, many patients are not eligible to undergo surgery. Given such considerations, it is not surprising that older BC patients are less likely to receive standard treatment. However, untreated disease may progress and severely impair quality of life and cancer-specific survival. Considering an individual’s life expectancy, goals and preferences, clinical decision-making must balance the benefits and risks of treatment against the morbidity and mortality arising from untreated or under-treated cancer.
It is easy to say, then, that older patents with MIBC tend to have poorer cancer-specific survival than younger patients, probably due at least in part to lower rates of radical treatment and perioperative chemotherapy[78].
Noon et al[78] investigated outcomes in more than 3000 cancer registry patients of all ages: five-years after diagnosis, 19% had died from BC and 19% from other causes, while for MIBC, the five-years cancer-specific mortality rate in this series was 49.7%. Within this cohort, older adult patients were significantly less likely than their younger counterparts to have undergone radical therapy for invasive cancer (12% among patients aged 80 years and older compared

to 52% in patients under the age of sixty) and exhibited higher cancer-specific mortality. The authors concluded that clinicians should consider offering more aggressive and potentially curative treatment to older but still sufficiently fit patients. These studies, along with clinical experience, suggest that there is extensive under-treatment of older adult patients with potentially curative MIBC.

The main issue to address is therefore the difference between the biological age and the chronological age of the patients. In the everyday clinical practice we face many levels of dependency or fitness and most of the times it depends on the age of the patients we are treating. However, there are differences even within the same population group when considering age. Though functional age is increasingly recognized as more important than chronological age, there is understandable concern about treatment-related complications due to co-morbidities, polypharmacy and poor physiological reserve. With increased age, functional reserve diminishes, resulting in a decreased resistance to stressors like surgery. These aspects can be summed up in two nearly new concepts: functional capacity and frailty. This is where we should really start when it comes to a proper 360 degrees care.

3.4.1 Functional capacity

Physiological functional capacity (PFC) refers to the ability to carry out daily physical activities and the ease with which these tasks are accomplished. As people age, even in good health, there is an inevitable decline in PFC, leading to a diminished ability to perform certain physical tasks. This decline can eventually lead to a higher risk of functional disability, greater reliance on healthcare services, loss of independence, and a reduced quality of life.

The measurement of functional capacity provides information that allows to examine the effects of disease on performance of an individual, to compare how specific diseases impact the ability to perform specific tasks, and how specific treatments such medications or psychosocial interventions, improve performance on skills critical to their lives.

Up to 50% of patients with advanced cancer may present impairments in functional capacity[79], and a decline during anticancer treatments was observed[80]: the outcomes in those patients are often not good enough to justify the treatment in the first place, even if the prognosis otherwise is poor.

Considering this, it becomes clear that a tailored, intensive, rigorous, and multidisciplinary approach is necessary, particularly for a compromised patient cohort such as those with bladder cancer. This approach should aim to preserve independence in daily activities and maintain quality of life. Currently, the practice involves assessing which patients are eligible for a specific treatment, whether pharmacological or clinical. This process often leads to the exclusion of a significant portion of patients who, due to age and physical condition, are not potential beneficiaries of the therapy. However, as previously mentioned, this is not the way patient care should be managed in the future, especially given the unstoppable and progressive aging of the population, which will present increasingly complex clinical profiles characterized by multiple comorbidities. The risk is that more invasive treatments, which are often the most effective, will benefit only a small segment of the population, marginalizing the broader landscape of oncological diseases.

Therefore, there are essentially two solutions: either make therapies less aggressive and less impactful for the patient, or more likely, make the patient better suited to undergo a complex treatment regimen. This is the vision that must be adopted for appropriate clinical practice in the future.

3.4.2 Frailty

Surgical risk is better estimated through comorbidities and geriatric parameters like the frailty index since they are associated with postoperative morbidity and mortality.
Frailty is a common condition among elder population, and it can highly affect clinical outcomes. Also, its prevalence will most likely increase in the future 30 years as life expectancy grows longer and longer. Frailty has been defined by major international scientific societies as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death"[81]. It is a clinical condition characterized by an excessive vulnerability of the individual to endogenous and exogenous stressors and it generates a high risk of developing negative health-related events. This implies, once again, that in the future geriatric medicine will concur at modernizing the old way of practicing medicine.
As frailty significantly increases postoperative complications, prolonged hospital stay and institutionalization in patients aged over 65, and also improves the predictive power of the ASA score, preoperative frailty assessment should be recommended[82].
In frail patients undergoing RC, 30-day mortality and incidence of Clavien-Dindo grade IV complications increased by 30% compared to non-frail patients[83]. For these reasons a geriatric evaluation (GA) must be part of the preoperative protocol. Although the value of such an approach has not been subjected to randomized controlled trial, comprehensive GA has face validity since it provides information on a patient's physical function, cognition, nutrition, comorbidities, psychological status, and sources of social support[84].
The SIOG Bladder Cancer Task Force accord broadly with the ASCO Expert Panel12 which in 2018 emphasized the need for GA to identify vulnerabilities not routinely captured in oncology assessment. This is a key point mainly because frailty is a dynamic entity able to improve or worsen over time: working on a multi-disciplinary plan focused both on a physical and psychological level, alongside a customized dietary implementation, is expected to optimize the patient overall status and helps achieve better surgical outcomes.

Frailty is of particular importance in cancer: the elderly makes up for a significant proportion of patients diagnosed with cancer and account for approximately 80% of cancer deaths each year in the United States[85]. Both cancer and the therapies that goes along are additional stressors that challenge a patient's physiological reserve, it is then safe to say that the incidence of frailty in older people affected by cancer is particularly high. It has been demonstrated that frail patients are at risk of postoperative complications, chemotherapy intolerance, disease progression and death[85].
Surgery is an essential component of oncological therapy, and it often represents the only curative option. A patient's fitness for surgery is the first and main assessment to establish when it comes to solid tumors as it occurs in bladder cancer. Since these patients' average age tends to be >70 years old[86] they are more likely to have a diminished physiological reserve and face postoperative morbidity and mortality, making the GA mandatory.

3.5 Hemoglobin status in oncological patients

Cancer-related anemia (CRA) is a common sign occurring in more than 30% of cancer patients at diagnosis before the initiation of antineoplastic therapy[87].
At this regard, it is important to differentiate between two main categories of cancer patients with anemia:

- those who have normal hemoglobin levels before starting treatment (they are usually candidate to undergo neoadjuvant chemotherapy), where anemia should be viewed as a treatment-related toxicity;
- the ones who are already anemic prior to beginning antineoplastic therapy where this is mostly a result of the chronic inflammatory status existing in advanced neoplastic patients.

Preoperative anemia in patients undergoing oncologic surgery is common and can be as high as 75% in certain cancers[88]. When it comes to RC, around half of bladder cancer patients are anemic at the time of surgery and in retrospective cohort studies a hemoglobin lower than 105 g/L is associated with decreased cancer-specific survival after RC and increased all-cause mortality[89].
A major negative impact of anemia is the reduced ability of erythrocytes to transport oxygen throughout the body, which compromises the patient's physical and psychological well-being. To counteract these changes, the body activates compensatory mechanisms that involve adjustments in the Hb-O2 dissociation curve, as well as the cardiovascular and renal systems. The primary compensatory response comes from the cardiovascular system, which works to reduce peripheral vascular resistance and increase stroke volume, thereby boosting cardiac output. Simultaneously, the kidneys respond to hypoxia by increasing the production of erythropoietin (EPO), a key regulator of red blood cell production. Signs such as palpitations and sinus tachycardia indicate increased cardiac output, while paleness, postural hypotension, and vertigo are associated with decreased erythrocyte mass and lower peripheral vascular resistance. Symptoms like dyspnea, headache, sleep disturbances, lethargy, depression, transient cerebral ischemia, angina pectoris, reduced functional capacity, and fatigue are linked to oxygen deficiency in various organs and tissues. In CRA, fatigue, weakness, and diminished physical and cognitive abilities are particularly prevalent. Additionally, CRA significantly impacts the central nervous system, which is especially sensitive to hypoxia. Anaemia related to cancer also weakens the immune system, leading to immunosuppression[90], which increases susceptibility to infections and reduces the effectiveness of antineoplastic treatments. This immunosuppression is largely due to the metabolic damage caused by hypoxia, which impairs lymphocyte function[91].

3.5.1 Pathogenesis of cancer related anemia (CRA)

More often detected in patients with advanced stage disease where it therefore represents a specific symptom of the neoplastic condition as a consequence of chronic inflammation, anemia is also frequently due to a malnutrition status and to neoadjuvant therapy that many oncological patients go through.

The pathogenesis is well known: proinflammatory cytokines, mainly IL-6, which are released by both tumor and immune cells, playing a pivotal action in CRA etiopathogenesis by they promoting alterations in erythroid progenitor proliferation, erythropoietin (EPO) production, survival of circulating erythrocytes, iron balance, redox status, and energy metabolism, all of which can lead to anaemia[87].

The main pathogenetic mechanisms by which inflammation may cause anaemia include[92]:

a) shortened erythrocyte survival in conjunction with increased erythrocyte destruction which is caused by mainly by macrophage activation by different proinflammatory stimuli;
b) suppressed erythropoiesis in bone marrow;
c) effects of inflammation on erythropoietin production due to a direct inhibitory cytokine action on the erythropoietic progenitors;
d) alterations in iron metabolism that result in iron-restricted erythropoiesis induced by hepcidin increase;
e) increased concentration of ROS providing for both the EPO deficit and erythrocytes fragility and maturation.

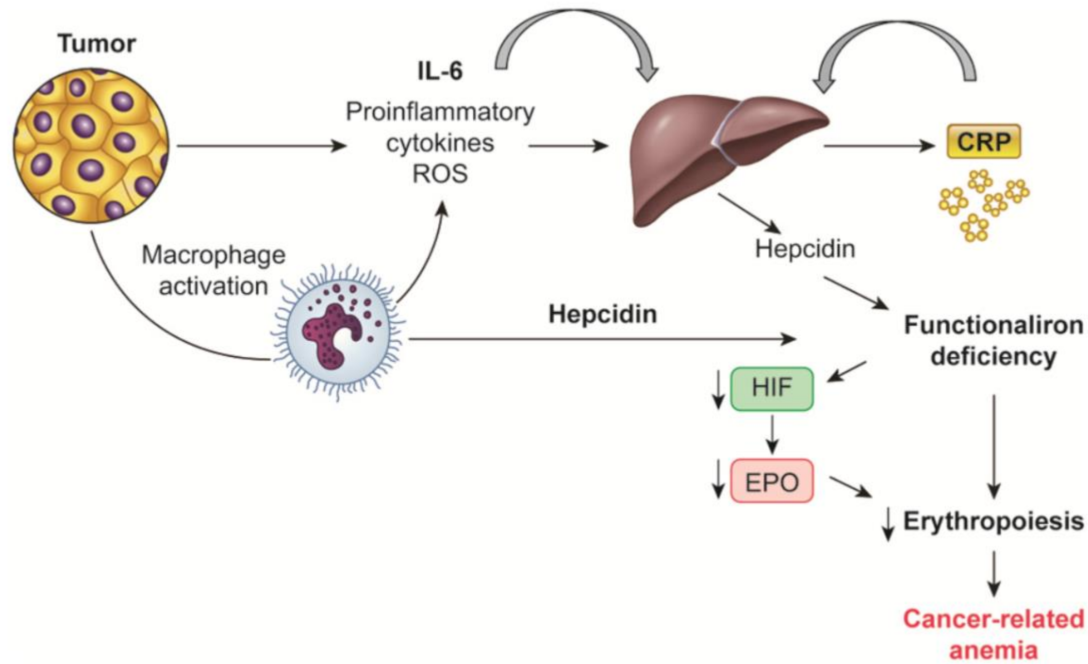

Figure 9 - Pathogenesis of cancer related anemia.

Cancer-related anemia is most often described as normochromic and normocytic, with a mean corpuscular volume (MCV) between 80–100 fl[93]. It also has a decreased circulating serum iron concentration and transferrin saturation despite ample iron stores. Usually it is a hypoproliferative anemia with a reticulocyte count below normal (<25,000/microL) and a low value of reticulocyte index (normal range between 1 and 2), which is a more accurate measure of the reticulocyte count corrected against the severity of anemia on the basis of hematocrit[94]. Additional features include normal/low serum iron concentrations (normal range 55–160 µg/dl for men and 40–155 µg/dl for women) and reduced total iron binding capacity (transferrin saturation <50%)5, whilst ferritin values may be normal (30–500 ng/ml) or more often increased (≥500 ng/mL), with increased iron storage. Additionally, bone marrow erythroid hypoplasia is characteristic of CRA, and circulating erythropoietin (EPO) levels, the primary growth factor for erythrocytes, are inappropriately low relative to the severity of anemia and the presence of normal renal function[92].

It is also known that anemia is a clinical indicator of a multi-factorial interplay between malnutrition, frailty and poor performance status.
As cancer progresses, patients often experience significant nutritional decline, marked by weight loss, muscle mass reduction, increased resting energy expenditure, and symptoms such as anorexia, nausea, and vomiting. These symptoms can be worsened if chemotherapy is adopted as a treatment. A large observational study has highlighted the importance of weight loss and BMI as significant negative prognostic factors in cancer patients, independent of other factors like tumor site, stage, and performance status: even a modest weight loss at diagnosis is associated with higher morbidity and mortality[95]. This weight loss is a key indicator of cancer cachexia, a complex syndrome driven by inflammation that frequently accompanies advanced cancer stages. The weight loss seen in cachectic patients is not merely due to reduced nutrient intake from anorexia; it is also driven by metabolic changes that increase resting energy expenditure. Chronic inflammation in cancer plays a critical role in these metabolic disruptions by altering glucose metabolism, lipoprotein lipase function, and protein synthesis, leading to muscle mass depletion. In cancer patients, muscle protein production decreases while proteolysis increases, in contrast to the liver, where the synthesis of acute-phase proteins like CRP, fibrinogen, and hepcidin increases despite stable or reduced albumin production. Malnutrition, alongside weight loss and reduced food intake, is strongly associated with anemia in chronic inflammatory diseases, suggesting that nutritional status plays a significant role in CRA development. In advanced cancer, anemia is typically associated with weight loss and metabolic changes driven by the disease. Thus, treating CRA may be more effective with a multifactorial approach that includes nutritional support. Supporting this view, studies have found an association between anemia and leptin, a key marker of nutritional and metabolic status. Leptin levels, which are inversely related to proinflammatory cytokines and cancer stage, have been shown to correlate with Hb levels in various cancers. Given that anemia in cancer patients is tied to nutritional factors that affect iron, vitamins, and other micronutrients essential for erythropoiesis, it is not surprising that leptin, a sensitive nutritional marker, is correlated with Hb levels.

3.5.2 CRA and cystectomy

Radical cystectomy is a complex and morbid surgery associated with prolonged hospitalization with up to 65% of patients experiencing at least one postoperative complication and 15% experiencing a high-grade complication[18]. It is associated with acute blood loss as the median blood loss during a RC is approximately 600ml and iron storage may be insufficient to restore perioperative Hb loss: up to 30% of patient may require transfusions perioperatively[96]. Moreover, preoperative anemia is associated with increased complications and prolonged hospital stay after colon surgery[97].
Approximately half RC patients are anemic at the time of surgery and a good amount of them also meets criteria for being malnourished, which increases even more the anemic risk. There is an association between preoperative anemia and post operative complications[97] thus RC patients face a 50% increase in risk of major adverse post-operative events within 90-days. Anemia is also an indicator of augmented frailty in this population[97] and that introduces the main point of this study: adopting a preoperative care that includes Hb levels correction and

nutritional support, such as in the multimodal prehabilitation we planned for our patients, may possibly decrease the anemic state and therefore the frailty rate, enhancing the physiological reserve and lastly minimizing the post-surgery complications. We believe that the presence of anemia can identify patients at higher risk for complications and be useful in preoperative counseling.

Anemia is defined by the World Health Organization as an Hb concentration <13 g/dL for men, <12 g/dL for non-pregnant women and <110 g/L for pregnant women[98].
These definitions are widely quoted and accepted, but they are suboptimal when it comes to major surgeries: women have lower circulating blood volumes than men, but the same procedures performed in either sex often result in comparable amounts of blood loss. Therefore, when measured as a proportion of circulating blood volume, blood losses are proportionally higher in women and may result in higher transfusion rates[99]. As women with a pre-operative Hb of 12 g/dL are twice as likely to require a transfusion as men with an Hb of 13 g/dL, this hemoglobin level should be considered as suboptimal in surgical settings. It is now emerging, then, that when treating anemia pre-operatively, the target hemoglobin concentration should be ≥ 13 g/dL in both sexes, to minimize the risk of transfusion-associated unfavorable outcomes[100]. It's easy to understand that, therefore, laboratory investigations should be performed as early as possible in the pre-operative period in order to implement the most appropriate treatment, if needed.
There is good evidence that attempts to correct iron deficiency anemia pre-operatively will improve Hb before surgery, but there is little good quality evidence.
Preoperative anemia should be corrected, generally through an iv iron formulation. This leads to a more rapid and complete response than the oral formulation. In older adult malnourished patients, vitamin B12 and folic acid are also recommended[100]. Whether preoperative erythropoietin improves outcome remains unclear. In Europe, it is approved only for orthopedic surgery with moderate to elevated blood loss; in the U.S. it is indicated for all major non-cardiac surgery.
Intraoperative transfusion of red blood cells (RBCs) leads to poorer cancer-related outcomes after RC.54 It is not clear whether transfusion is causally related to poor outcome or simply a reflection of higher risk disease. A Hb target of around 8 mg/dL for fit patients and 9 for the frail seems appropriate to lower major short-term complication[85].

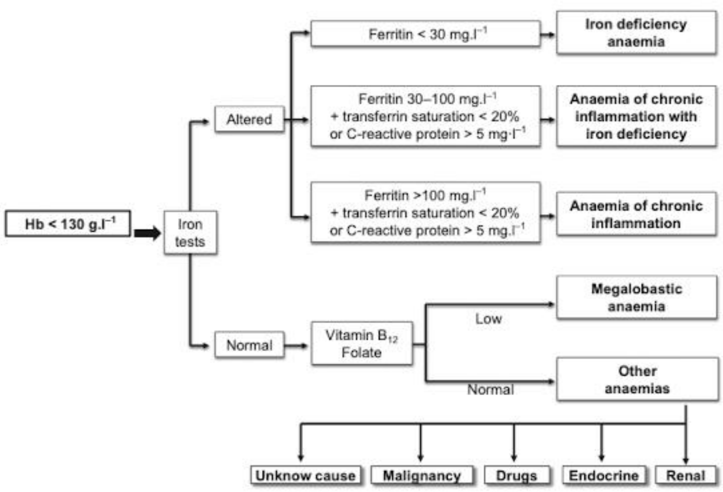

Figure 10 - Algorithm for classification of peri-operative anemia.

4 Aims of the study

Currently there is no robust evidence demonstrating that a multidisciplinary training of the patient prior to surgery, including many different branches such as nutrition, psychology and physical training and anemia correction, significantly improves postoperative clinical outcomes. Nowadays there is a lack of studies evaluating the influence of preHAB on postoperative outcomes.
We hypothesize that an individualized and intensive prehabilitation program, conducted over 4 weeks prior to a radical cystectomy (with or without neoadjuvant chemotherapy) for bladder cancer may improve patients' functional capacity and hemoglobin, and therefore, it may reduce the number and severity of postoperative complications, enhancing clinical recovery and outcome.

The aims of Our investigation are:

i. describing the improvement in functional capacity analyzing the trend of hemoglobin in patients undergoing preHAB which includes personalized physical exercise, nutritional support, and psychological care;
ii. exploring if preHAB affects the hemoglobin status in anemic and non-anemic patients;
iii. evaluating how Hb levels link with postoperative complications in anemic and non-anemic patients.

5 Materials and methods

5.1 Patient population

In the Prehabilitation Program, oncological patients undergoing major surgeries with a predetermined high complication index have been included. This circumstance implies a physical deterioration of the individual, potentially leading to extended hospitalization in the Post-Surgical Critical Care Unit. The doors of the Service were opened on November 15, 2023, and to the 31/05/2024, a total of 234 patients have been enrolled. A maximum of 380 patients has been set as the yearly limit that the team can accommodate. Patients have been selected from a range of surgical subspecialties including general surgery, gynecology, urology, maxillofacial surgery, and otorhinolaryngology.

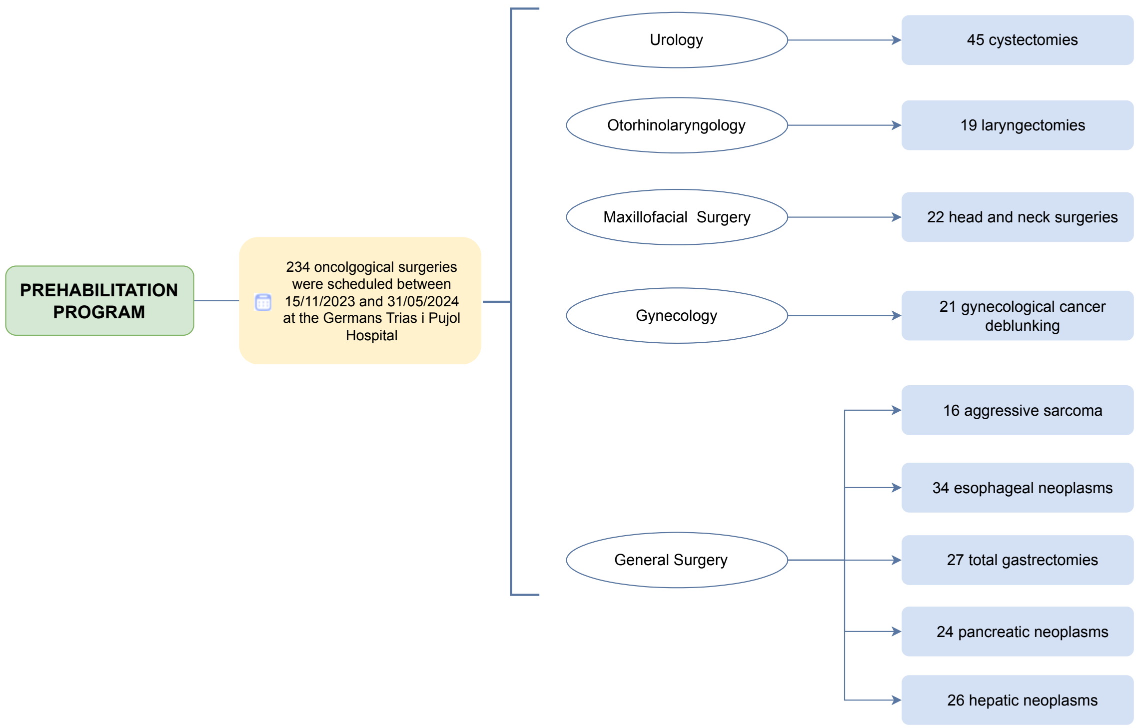

Figure 11 - Prehabilitation program overview.

The inclusion criteria adopted to determine which patients were eligible to undergo the prehabilitation program are as follows:

- Diagnosis of neoplasia;
- Aggressive surgical treatment implying postoperative intensive care unit admission;
- ≥ 4 weeks between diagnosis and surgery date;
- Pending of one of the following specialties with surgical indication as listed:
  a) General Surgery:
    (i) Esophageal neoplasia
    (ii) Total gastrectomy
    (iii) Hepatic neoplasia
    (iv) Sarcoma

b) Gynecology:
    (i) Debulking in ovarian cancer
c) Urology:
    (i) Radical cystectomy
d) Maxillofacial Surgery:
    (i) Head and neck cancer
e) Otolaryngology:
    (i) Laryngectomy

- given consent to participate in the study;
- age >18 years old;
- no metastases;
- no psychiatric disorders;
- no contraindications to physical exercise;
- no language barrier.

The exclusion criteria, instead, are as follows:

- sudden emergency/urgent surgery;
- presence of metastasis;
- age <18 years old;
- diagnosis of psychiatric disorder;
- lack of consent to participate in the study;
- not having 4 weeks prior to the surgery date;
- contraindications to physical exercise;
- language barrier;
- deterioration of general conditions during preHAB;
- death.

During the period between November 15th 2023 and June 30th 2024, time frame examined in this study, a total of 45 eligible patients were identified for recruitment.
Among these, 22 were excluded: 6 refused to participate in the trial; 4 underwent emergency surgery without completing the four-week pathway; 4 developed complications incompatible with the continuation of the study; 6 withdrew, and 2 died.

Net of introducing 45 patients into the study, 23 underwent radical cystectomy, also known as the Bricker procedure, forming the organic basis on which the focus of this report is developed.

5.2 Preoperative data

N°	Medical history n.	Sex	Surgery	Start preHAB	End preHAB	Surgery date
1	15945209	♂	Bricker	15/11/2023	29/11/2023	12/12/2023
2	103414	♀	Bricker	22/11/2023	20/12/2023	09/01/2024
3	15828604	♂	Bricker	22/11/2023	13/12/2023	15/12/2023

4	492617	♂	Bricker	22/11/2023	20/12/2023	30/01/2024
5	159817	♂	Bricker	29/11/2023	03/01/2024	09/02/2024
6	12025381	♀	Bricker	29/11/2023	03/01/2024	02/02/2024
7	14749807	♂	Bricker	29/11/2023	03/02/2024	13/02/2024
8	269629	♀	Bricker	13/12/2023	10/01/2024	24/01/2024
9	15347150	♂	Bricker	20/12/2023	17/01/2024	31/01/2024
10	11459	♀	Bricker	20/12/2023	17/01/2024	19/01/2024
11	73425	♂	Bricker	10/01/2024	31/01/2024	14/02/2024
12	17567794	♂	Bricker	10/01/2024	31/01/2024	13/03/2024
13	46320	♂	Bricker	17/01/2024	07/02/2024	20/02/2024
14	15923320	♂	Bricker	17/01/2024	07/02/2024	21/02/2024
15	15820533	♂	Bricker	17/01/2024	07/02/2024	23/02/2024
16	18690379	♀	Bricker	24/01/2024	14/02/2024	02/03/2024
17	14797885	♂	Bricker	07/02/2024	28/02/2024	15/03/2024
18	23514	♀	Bricker	07/02/2024	28/02/2024	13/03/2024
19	203835	♀	Bricker	14/02/2024	06/03/2024	25/03/2024
20	18664660	♂	Bricker	21/02/2024	13/03/2024	28/03/2024
21	11600374	♂	Bricker	28/02/2024	13/03/2024	04/04/2024
22	34498	♂	Bricker	13/03/2024	10/04/2024	19/04/2024
23	113376	♂	Bricker	20/03/2024	17/04/2024	24/04/2024

Table 1 – Demographic of the studied population.

Among these, specific clarifications are required:

- 15 were identified as pre-frail (PFP) and did not undertake a dedicated training program supervised by the team's physiotherapist;
- 8 were identified as frail (FP) and were invited to train twice a week on-site under the supervision of the team's physiotherapist;
- 12 were overweight and embarked on a hypocaloric and hyperproteic diet with the support of appropriate dietary supplements;
- 11 were underweight and embarked on a hypercaloric and hyperproteic diet with the support of appropriate dietary supplements;
- 16 had hemoglobin levels below 13 g/dL and were selected for correction of anemia through intravenous iron infusion.

We recorded full medical and personal history, information about the overall patient's fitness, basic physical measurements and the following data:

- blood sample to evaluate hemoglobin, HbA1c, albumin, ferritin and transferrin saturation levels;
- height;
- weight;
- electrocardiogram;
- blood pressure;
- bioimpedance;
- residual functional capacity;

- diary level of activity;
- sleep quality;
- depression level;
- inspiratory and expiratory muscle strength (MIP).

5.3 Enrollment procedure

Once the surgical team provides the indication for surgery, the patient's data will be sent to the Anesthesia Service at the Germans Trias i Pujol University Hospital (HUGTiP), where the inclusion criteria will be assessed, and any contraindications to participation in the study will be evaluated. Subsequently, the patient will be contacted by phone by the Complex Unit of Anesthesia and Resuscitation the week before the scheduled start of prehabilitation. They will be invited to participate in the study, providing detailed information about the trial's characteristics and strengths.
If the patient gives his consent, he will be invited to attend the Rehabilitation Department's outpatient clinics on the following Wednesday to sign the informed consent form and start prehabilitation.

The patients will be categorized into two groups: frail patients (FP) and pre-frail ones (PFP).
Initially, patients will be classified as Frail or Pre-frail based on the surgical magnitude and age, although this classification may be adjusted following stratification tests and the initial patient visit, which may reveal additional factors not captured by the initial assessment scales.

Each week, four new patients will be enrolled in the frail program, and an additional four will participate in the pre-frail program, resulting in a total of eight patients entering the trial each week.
The Multimodal Prehabilitation Program will span four weeks.

All patients, both frail and pre-frail, will receive visits from the anesthesiologist, the anesthesia nurse, a nutritionist and a physiotherapist. Frail patients will also receive visits from a physiatrist and a team of psychologists.

5.4 Frail patient management

Frail patients (FP) receive optimized treatment from a nutritional, physical, and mental/emotional perspective. FP will then attend the Unit every Wednesday afternoon during these four weeks for group workshops and face-to-face follow-ups.

Beginning with the nutritional aspects, the patient is attended by a nurse who will administer the Mini Nutritional Assessment -Short Form (MNA-SF) score and the Malnutrition Universal Screening Tool (MUST) during the welcome session. Patients then will be assessed in an hour group session by the nutritionist, who will provide general recommendations.
For patients with MUST scores > 2 or MNA-SF scores >12, a post-exercise protein supplementation will be provided along with written recommendations.

If any patient necessitates personalized supplementation (MUST score ≤ 2 or MNA-SF score <1), tailored nutritional support will be provided and they will be referred to the nutritionist for customized calorie and protein supplementation as deemed necessary.
For what concerns the first visit with a physiatrist and a physiotherapist, based on each patient's results, an individualized physical activity plan will be designed, followed jointly at the PreHAB Unit on Wednesday afternoons and at the Rehabilitation Service on Monday and Friday mornings.

Measurement of the maximal inspiratory pressure (MIP) for respiratory physiotherapy optimization will be conducted. Aerobic capacity will also be measured with an ergospirometry session per week, especially in the most frail patients. If deemed necessary for more than one patient, it will be scheduled in the morning at the Rehabilitation Service.

The first visit with a psychologist digs on FP's anxiety and depression caused by the scheduled surgery. A psycho-educational psychological intervention focused on reducing cognitive and emotional overload will be offered.
During the second, third, and fourth week, group workshops will be conducted by the physiotherapist and psychologist for about eight patients each.

During their attendance at the Prehab Unit, weekly verbal follow-ups will also be conducted by an anesthesia nurse to address any doubts or to handle any incidents.
Follow-up on requested complementary tests or specialist visits, if necessary, will be discussed with the anesthesiologist.
During last visit at the PreHAB Unit, on the 4th week, FP will participate in a group physiotherapy session and psychological support workshops. The physiotherapist will once again measure both the 6-minute walk test and the hand grip.
At the end of the programm will also deliver a satisfaction questionnaire of the prehabilitation program.
Finally, the anesthesiologist will assess the nutritional status, check the anemia recovery through blood tests and they will complete the preoperative evaluation.

5.5 Pre-frail patient management

Patients classified as pre-frail (PFP) will continue to have access to all services offered by different specialists, however, they will follow a more flexible regimen during the program: face-to-face sessions are disposed of in the first and fourth week, while telephone follow-ups are adopted in the intercurrent time.

They receive nutritional care at the Functional Units and will be followed by a nutritionist to provide individualized optimization in a similar way to the FP.

About physical fitness, during the welcome session the physiatrist will measure the maximal inspiratory and expiratory pressure (MIP) for respiratory optimization.
The 6-minute walk test will be performed by the physiotherapist, followed by a group training session where exercises will be explained according to stratification groups to be performed at home and/or at the collaborating gym in Badalona for those patients who desire so. The

suitability of conducting telemedicine physiotherapy sessions has been evaluated and will start later on this study.

When it comes to psychological care, the anxiety levels will be assessed using both the Pittsburg Sleep Quality Index and the Beck Depression Inventory (BDI) during the first visit, administered by a psychologist. Simple mindfulness tips will be provided, and specific websites will be recommended. If any PFP specifically requires reinforcement in this area, they will be added to the Unit's group workshops once a week.

The PFP will all be scheduled to attend the office on Wednesdays only on the first and fourth week. If a patient wishes to participate in more activities, they may attend in-person group workshops for physiotherapy and/or psychology during the entire program's duration.
Throughout the four-week duration of the PreHAB program, an anesthesia nurse will conduct telephone follow-ups to address any concerns, provide reinforcement, or manage any incidents that may arise. Any follow-up required for requested complementary tests or specialist visits will be coordinated with the anesthesiologist.
During the final visit to the Prehab Unit in the fourth week, the physiotherapist will conduct a reassessment, including the 6-minute walk test and hand grip evaluation, and distribute the program satisfaction survey.

An integrated data collection system will be implemented within the hospital's SAP system as part of the preoperative process: this system is a tool for quality control and it allows us to evaluate the overall impact of our project.

5.6 Project Execution Strategy

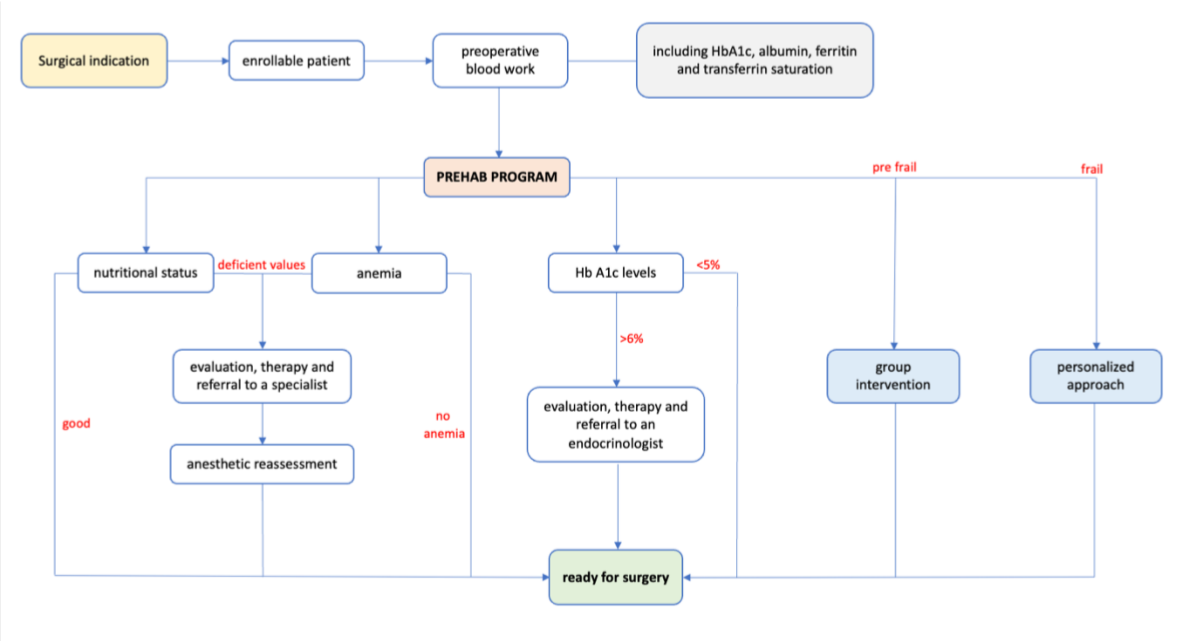

Figure 12 – PreHAB enrollment and outline of the operational plan.

5.7 Project Resources

The Multimodal Prehabilitation program derives its strength from not only the clinical improvement of patients but also from its holistic approach. To achieve this goal, the program addresses three main aspects: physical exercise, nutrition, and psychological support.

The organizational structure established for this study comprises a team based on:

- 1 anaesthesiologist;
- 1 anaesthesia nurse;
- 1 physiatrist;
- 1 physiotherapist;
- 1 nutritionist;
- 1 psychologists;
- 1 administrative staff.

Regarding physical resources, the spaces of the Rehabilitation Service, including the necessary gym and offices, have been made available by GTiPH. These spaces were utilized during Monday and Friday mornings and Wednesday afternoons.

The material resources and tools selected to ensure efficient patient care and treatment are listed in Table 2.

Professional	Tools and materials
Anesthesiologist	Integrated data collection (SAP) Informed consent forms Iron infusion (intravenous) Oral and written information questionnaire 1 computer
Psychologist	BDI and PSQI questionnaires 1 computer
Physiatrist	IPAQ questionnaire Respiratory pressure meter Fried scale Clinical frailty scale POWERbreathe Medic Plus® 1 computer
Physiotherapist	Portable pulse oximeter Stopwatch Borg RPE scale 2 cones (to measure the distance covered) Trundle wheel 1 chair *10-meters stretch of unimpeded walkaway*
Nurse	12-leads electrocardiograph Weighing scale with height measurement Digital blood pressure machine Preoperative analysis

	Complementary tests at the 1st visit 1 computer
Nutritionist	Diaries for physical and dietary activity MNAS and MUST questionnaires 2 Medical hand grip dynamometers InBoby S10 Water Composition Analyzer Protein shakes Hypocaloric shakes Immunonutrition shakes 1 computer

Table 2 - Equipment used by each professional.

5.8 Ethics committee approval

The Research Ethics Committee (CEI; Comité de Ética de la Investigació) of HUGTiP, chaired by Dr. Magí Farré Albaladejo, determined that the requirements established by current regulations for the execution of the present study were met. More details are reported on the table below:

Study code	INMUNOPREHAB 1.0
CEI Ref.	PI-24-090
Title (OG version)	*Inmunomonitorización de biomarcadores en pacientes frágiles sometidos al programa de prehabilitación multimodal previa cirugía mayor oncológica. Estudio piloto. Versión 02.0 (24/04/2024)*
Sponsored by	Hospital Universitari Trias i Pujol

ICO Institut Català d'Oncologia

IGTP Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol

5.9 Clinical evaluation test

The comprehensive assessment of patients selected for multimodal PreHab begins with the measurement and analysis of the individual's baseline characteristics. The clinical study of the patient spans both physical and emotional/psychological dimensions. To enable this holistic view of the individual, each patient underwent the following assessments:

- Weight, height, blood pressure measurements and BMI;
- Blood work;
- ECG
- bioimpedance
- MNAS/MUST questionnaires
- handgrip test
- IPAQ questionnaire
- Fried's frailty scale

- Clinical frailty scale (CFS)
- SPPB
- 6MWT
- Borg RPE scale
- PIM
- BDI and PSQI questionnaires

5.9.1 Demographics

Basic physical measurements were collected by the team nurse and recorded in the SAP portal. For weight and height, a digital scale equipped with a measuring rod was used to simultaneously assess the two values, expressed in kilograms (kg) and meters (m) respectively. The data were then related to each other to obtain the patient's BMI using the formula provided below:

$$BMI\ (\frac{kg}{m^2}) = \frac{weight\ (kg)}{[height\ (m)]^2}$$

BMI, or body mass index, is a quick, convenient, and inexpensive marker of health[101], used as a screening method for weight categories: underweight, healthy weight, overweight, and obesity. BMI has proven validity as a convenient and simple proxy for modeling the population-level association between obesity and increased mortality and morbidity[102].

Blood pressure was assessed using an arm multiparametric digital sphygmomanometer. The values, including diastolic blood pressure, systolic blood pressure, and heart rate, were collected with a single or series of 2 measurements, depending on whether the result was deemed invalid or affected by artifacts by the staff.

5.9.2 Blood sample analysis

Blood analyses were collected through venous blood sampling performed by the nurse at three different time points:

- T1= Week 1 - on the first visit at the beginning of the PreHab program;
- T2= Week 4 - end of the program;
- T3= at discharge.

The main values analyzed were:

- Hemoglobin
- HbA1c
- Transferrin saturation
- Ferritin

The evaluation of hemoglobin levels and the management of anemia are the key points of this study. All patients, regardless of gender, presenting with anemia defined by Hb levels

<13g/dL were treated with intravenous iron therapy. This decision was made despite the World Health Organization (WHO) defining anemia as a hemoglobin level less than 13 g/dL in men and 12 g/dL in women[98]. Intravenous iron therapy was administered as a one-time treatment within the first week of PreHAB initiation, facilitated by the cardiology department's referral of the patient. This therapy is the gold standard for normalizing anemia levels within a short timeframe, as it has been demonstrated that ferritin saturation and therefore Hb levels increase within the range of 2-4 weeks[103]. Since ferric carboxymaltose can lead to renal phosphate depletion and consequently hypophosphatemia[103], a supplement is also administered concurrently with iron therapy to correct this side effect.

Correcting anemia was our priority as there is a known intrinsic relationship with major intra and post-surgical complications, particularly cardiac complications. A study by Wu and Schifttner confirms the relationship between anemia levels and poor surgical outcomes due to cardiac complications, emphasizing that the majority of deaths can be attributable to only modest degrees of anemia (hematocrit levels of 27.0%-38.9%)[104].

Considering the high prevalence of diabetes and glucose intolerance across the population, it is reasonable to screen all individuals for HbA1c levels in the preoperative period. Post-surgical complications that may arise have been extensively described in the literature: the cutoff was set at an HbA1c of 6%, with levels lower than 7% associated with shorter length of stay, lower postoperative blood glucose levels, and a lower number of neurological complications and infections, but a higher number of reoperations[105]; or increased risk of infection and late-term mortality with levels above 6%[106].

5.9.3 MNA-SF and MUST questionnaires

There are several reports which document the impact of malnutrition in postoperative outcomes in the elderly[104]. Patients at nutritional risk have a higher rate of postoperative complications, higher mortality and a longer hospital stay[107]. In addition to that it is also known that the physiological stress induced by surgery often triggers a catabolic state, particularly pronounced in older individuals.
The latest guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) regarding perioperative nutrition highlight that BMI, alongside indicators such as unintentional weight loss, anorexia, decreased oral intake, and severity of comorbidities, serve as the primary criteria for identifying patients at heightened nutritional risk[108].
The PreHAB program firmly believes that preoperative nutritional optimization enhances positive surgical outcomes, to the extent that it constitutes one of its three main pillars.
In the absence of a definitive method to diagnose malnutrition, two questionnaires have been adopted for the assessment of nutritional status and the risk of malnutrition: il The Mini Nutritional Assessment – Short Form (®MNA-SF) e il Malnutrition Universal Screening Tool (MUST).

The MNA-SF is a validated tool widely utilized in healthcare settings, developed by Nestlé, it evaluates aspects of nutritional health such as:

- dietary intake its recent changes

- mobility
- psychological stress
- neuropsychological problems
- BMI

By incorporating these multifaceted assessments, the MNA-SF provides a comprehensive understanding of an individual's nutritional status and identifies potential malnutrition or risk factors for malnutrition. Due to its simplicity and reliability, it has become a cornerstone in geriatric nutrition assessment.

The MNA consists of a comprehensive evaluation comprising not only a questionnaire, but also a physical assessment: this includes assessments of BMI and grip strength. These measurements provide valuable insights into muscle mass, fat distribution, and overall physical function, which are crucial indicators of nutritional health, particularly in older adults. Based on the responses and findings, the MNA-SF generates a total score that categorizes individuals into different nutritional status categories, such as well-nourished (score >11), at risk of malnutrition (score 11-8), or malnourished (score <8). This classification helps healthcare professionals identify individuals who may require nutritional interventions and it aids the making process regarding nutrition interventions tailored to the specific needs of each patient .

We parallelly adopted the MUST questionnaire, which is a four-step screening tool, largely diffused in hospitals and care settings[109], that also identifies adults who are malnourished, at risk of malnutrition or obese. It as well includes management guidelines which can be used to develop a care plan. Its 4 steps consist in:

1. height and weight measurements in order to elaborate a BMI score;
2. assess the percentage of unplanned weight loss and score;
3. establish acute disease effect and score;
4. add scores for the previous steps to obtain the overall risk of malnutrition.

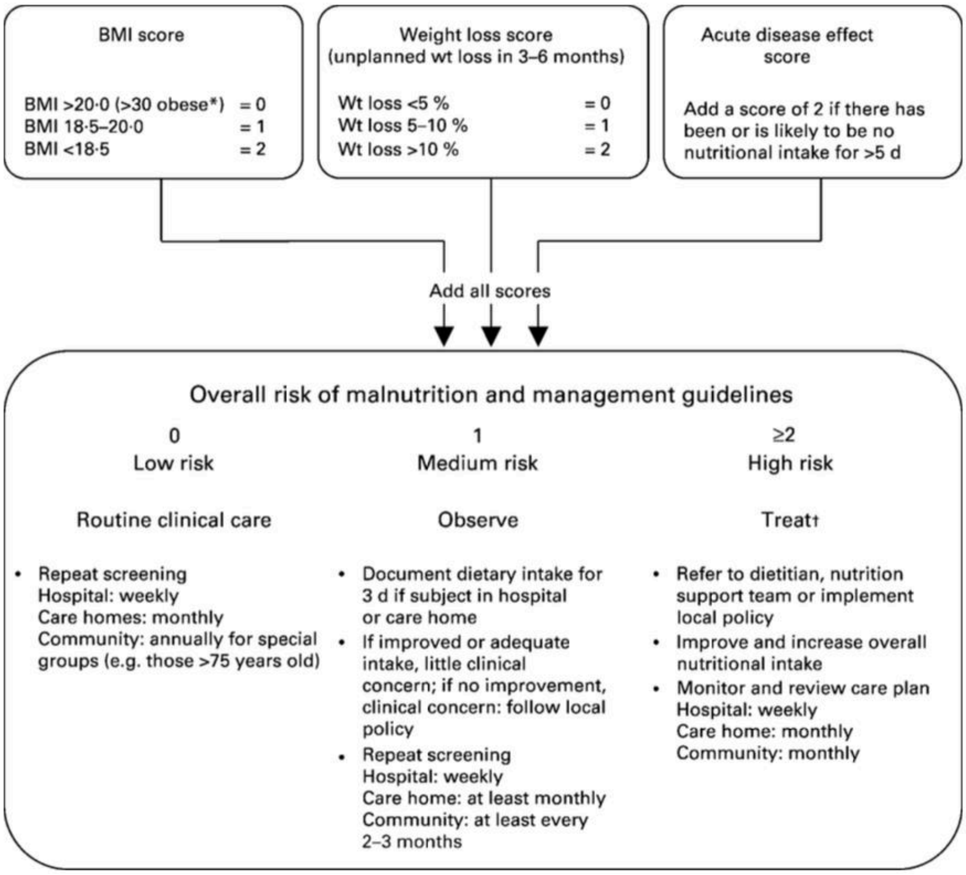

Figure 12 - The 'Malnutrition universal screening tool' for adults.

5.9.4 Grip test

Within the tests aimed at assessing physical strength, the grip test was adopted: also known as handgrip strength test, it is a medical assessment used to measure the strength of a person's hand and forearm muscles. During the test, the patient grips a dynamometer, a device specifically designed to measure grip strength, with their dominant hand. The dynamometer records the maximum force exerted by the individual while squeezing. This measurement provides valuable information about the individual's overall muscle strength, particularly in the upper extremities. Grip strength is often considered a reliable indicator of overall muscle function and physical performance[110], and it can be used to assess a person's functional status, nutritional status, and risk of certain health conditions, such as frailty (it is in fact one of the Fried Scale evaluation criteria), vascular and respiratory disease, cancer and overall mortality[111,112,113].

A manual dynamometer was used to assess grip strength. The test was conducted with the participant seated on a chair, forearms resting on a flat surface (as a table or the chair armrests), lower limbs resting on the ground while the shoulder of examined limb remained adducted and neutral for rotation, with the elbow flexed at 90 °, the forearm neutral for pronosupination and wrist extension between 0°-30° with 0°-15° of ulnar deviation. During the test, constant verbal encouragement was given to the participants to use their maximum strength. The test was repeated three times to obtain the mean.

5.9.5 IPAQ questionnaire

The International Physical Activity Questionnaire -Elderly- Short Form (IPAQ-E-SF) is a comprehensive tool designed to assess an individual's physical activity levels across various domains of daily life.
The questionnaire was administered by the physiatrist during the welcome visit and comprises 4 inquiries regarding the preceding seven days:

- Amount of sedentary time;
- Duration of walking time;
- Duration of moderate physical activity;
- Duration of vigorous physical activity.

For each of these activity types, the questionnaire collects information on frequency (measured in days per week) and duration (time per day) separately, providing a detailed overview of the individual's physical activity patterns.
This test was structured to provide separate scores on walking; moderate-intensity; and vigorous-intensity activity as well as a combined total score to describe overall level of activity. Computation of the total score requires summation of the duration (in minutes) and frequency (days) of walking, moderate-intensity and vigorous-intensity activities.

5.9.6 Fried’s Frailty Score and Clinical Frailty Scale

We adopted two of the most reliable assessments to evaluate the patient population frailty: the Fried’s Frailty Score and the Clinical Frailty Scale (CFS). These are fundamental tools that allowed us to understand in which of the two groups, FP and PFP, to place the patient to ensure appropriate management and optimal effectiveness of the program.
The Fried Frailty Scale, also known as the CHS index, it considers frailty by its physical characteristics, or ‘phenotype’, defining the condition as the presence of at least 3 conditions out of 4 as shown in Figure 13: shrinking (unintentional weight loss of 4.5 kg or more in the last year), weakness (low grip strength), exhaustion (self-reported), slowness (slow walking speed) and low physical activity.

A. *Characteristics of Frailty*	B. *Cardiovascular Health Study Measure**
Shrinking: Weight loss (unintentional) Sarcopenia (loss of muscle mass)	Baseline: >10 lbs lost unintentionally in prior year
Weakness	Grip strength: lowest 20% (by gender, body mass index)
Poor endurance; Exhaustion	“Exhaustion” (self-report)
Slowness	Walking time/15 feet: slowest 20% (by gender, height)
Low activity	Kcals/week: lowest 20% males: <383 Kcals/week females: <270 Kcals/week
	C. *Presence of Frailty*
	Positive for frailty phenotype: ≥3 criteria present
	Intermediate or prefrail: 1 or 2 criteria present

Figure 13 – Characteristics of Fried's frail phenotype.

On the other hand, the CFS is not merely a questionnaire, it is a method to condense data gathered during a clinical encounter with an elderly individual, particularly valuable for screening and providing an estimate of the individual's overall health status.

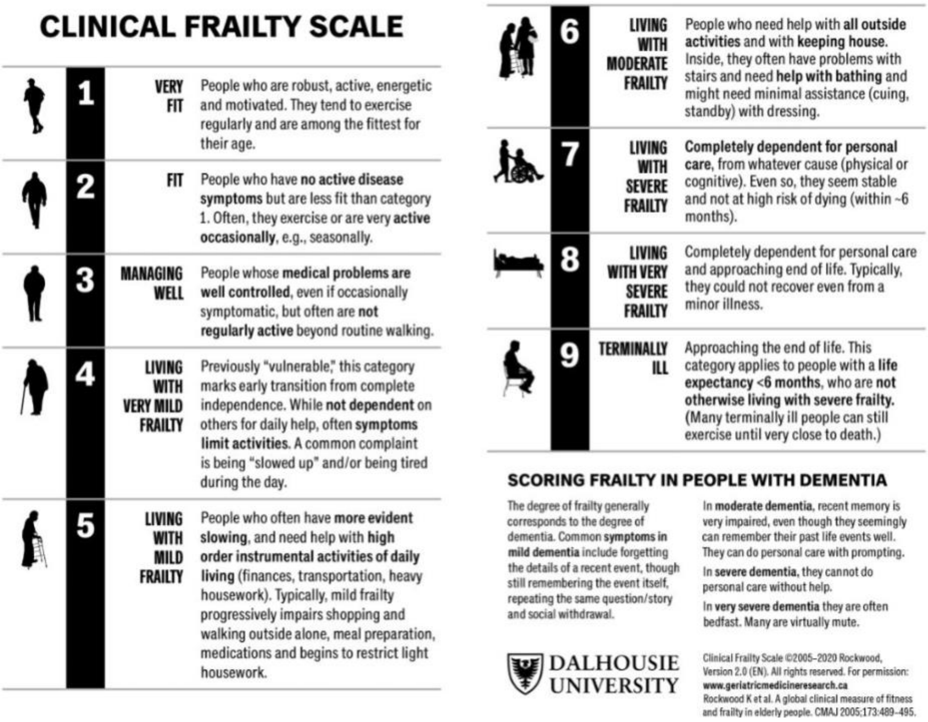

Figure 14 - Clinical Frailty Scale.

5.9.7 Six minute walking test

The 6-Minute Walking Test serves as an exercise assessment to evaluate aerobic capacity and endurance.
To conduct the test, a 30-meter obstacle-free space was prepared in the Rehabilitation Service corridor, marked by cones at the path's ends. Before initiation, the physiotherapist measures the participant's pulse rate, blood pressure and oxygen level.
The participant first rates his resting physical exertion using the Borg Rating of Perceived Exertion (RPE) scale (Figure 15). Then he briskly walks back and forth along the designated path for 6 minutes, striving to cover the greatest distance achievable. Participants may slow down or rest as needed but are encouraged to push for their optimal performance. They are trained to report any respiratory symptoms or chest pain, which are noted for reference. Throughout the test, participants wear a pulse oximeter, with blood oxygenation and heart rate being recorded at the starting point and then every minute. At the end of the test, participants reassess their perceived exertion using the Borg scale. It's noted that healthy

Borg RPE scale®
- Rating of Perceived Exertion

6 No exertion at all
7 Extremely light
8
9 Very light
10
11 Light
12
13 Somewhat hard
14
15 Hard (heavy)
16
17 Very hard
18
19 Extremely hard
20 Maximal exertion

Figure 15 - Borg scale: Rating of Perceived Exertion

adults typically achieve a score between 400-700 meters, with higher scores indicative of superior performance.
It has been shown that the 6MWT is significantly associated with mortality risk[114], making it a key tool in our study.

5.9.8 Short Physiscal Performance Battery

The Short Physical Performance Battery (SPPB) is another widely used tool for assessing physical function, particularly in older adults. It consists of three parts performed in the following order:

- balance test in three positions: feet together, semi-tandem, and tandem (as shown in figure 16), kept for 10 seconds each;
- gait speed test over 4 meters;
- chair stand test of rising from a chair 5 times.

Each element of the SPPB is graded on a scale of 0 to 4, with higher scores reflecting superior physical function. These individual scores are combined to generate a total score ranging from 0 to 12. Widely utilized in both clinical and research settings, the SPPB serves as a valuable tool for assessing physical performance and predicting outcomes such as disability and mortality[115].

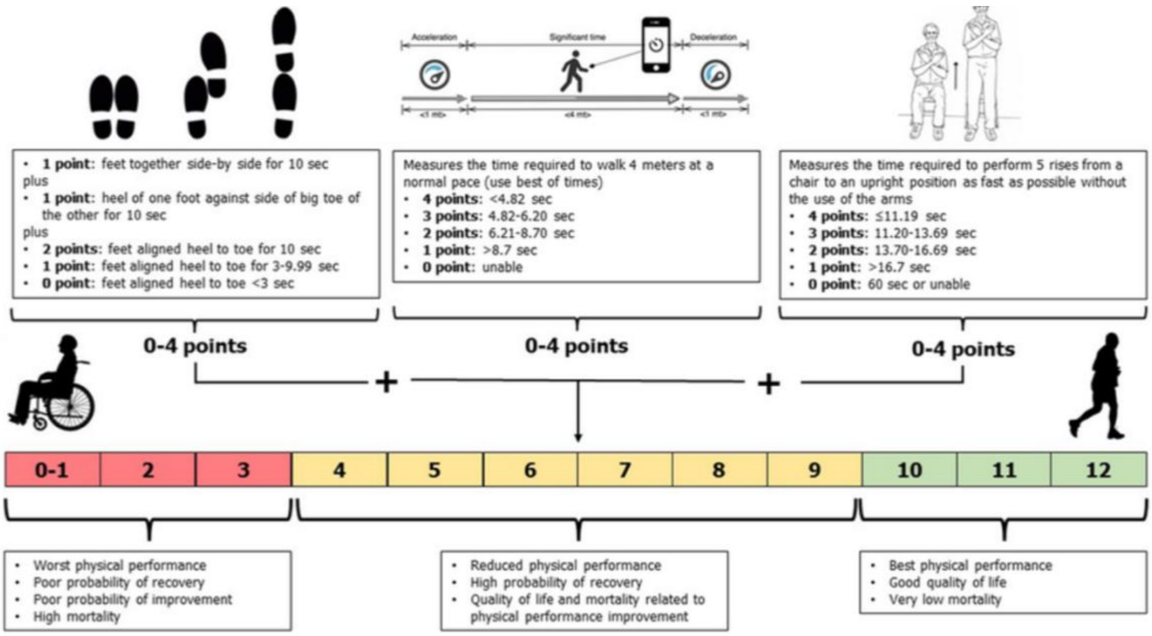

Figure 16 - Description and interpretation of SPPB scale.

5.9.9 Pittsburgh's Sleep Quality Index (SPQI) and Beck's Depression Inventory (BDI)

During the first session with the psychologist, two questionnaires are administered to each patient to assess respectively the quality of sleep and a possible depressive state. Sleep is analyzed through the PSQI, a tool that assesses: subjective quality of sleep, difficulty falling asleep, duration, efficiency, sleep disturbances, use of hypnotic medications, and impairment of daytime activities due to fatigue. This questionnaire has been validated with a variety of

clinical populations, including patients with major depressive disorder, disorders of initiating and maintaining sleep, disorders of excessive somnolence, cancer[116], and fibromyalgia.
Subsequently, all patients are administered the BDI, a questionnaire consisting of 21 questions that address and quantify themes such as: sadness, pessimism, failure, loss of pleasure in daily activities, feelings of guilt, feelings of punishment, self-esteem, self-criticism, suicidal ideation, crying, agitation, loss of interest, indecision, self-evaluation, loss of energy, sleep disturbances, irritability, changes in appetite, difficulty concentrating, fatigue, and decreased libido with a score ranging from 0 to 3. A score of 20 or above begins to delineate a profile of mild depression which can be addressed with the initiation of psychotherapy, always carried out within the PreHAB program.

5.10 Statistical Analysis

Patient characteristics were described, at the different time-points of the study, with frequencies with percentages for categorical variables and median and interquartile range (IQR) for continuous variables.
The statistical tests used to observe the differences in the distribution of the variables according to whether the patients had anaemia or not, were the Kruskall-Wallis test for continuous variables and the Chi-squared test or exact Fisher test when the expected frequencies is less than 5.
All statistical analyses were performed with the R v. 4.2.0 statistical software.

6 Results

6.1 Demographic chart

The demographic details of our dataset are summarized in detail in the Table 3. Our population counts 23 patients: the mean age at admission is 71.5 years (±8.27), the mean BMI is 28.1 (±4.20), the mean hospital stay accounts for 9 days and the mean hemoglobin level before starting the preHAB (t0) program was 11.3 g/dL.
Out of 23 patients, 16 (69.6%) were anemic and 7 had Hb levels >13g/dL.
A total of 8 patients (34.8%) were considered frail and attended the training courses hosted by our physiotherapist at the hospital, while 15 patients (65.2%) were assessed as pre-frail.

	Total
	N=23
Gender, n (%)	
female	7 (30.4%)
male	16 (69.6%)
Weight (kg), median [IQR]	78 [63.6 ; 85.4]
Height (cm), median [IQR]	164 [158.5 ; 171.0]
BMI, median [IQR]	28.1 [24.6 ; 32.4]
Birthday, median	15 August 1952
Barthel scale, median	100.0
Age at admission (years), median	71.5 [64.6;76.2]
Lenght of hospital stay (days), median	9
Chemotherapy, n (%)	
yes	12 (52.2%)
no	11 (47.8%)
Hemoglobin before preHAB (t1)	
(g/dL), median [IQR]	11.3 [10.8 ; 13.7]
Hb <13 g/dL, n (%)	
yes	16 (69.6%)
no	7 (30.4%)
Hemoglobin at the end of the preHAB (t2)	
(g/dL), median [IQR]	12.1 [10.6;13.1]
Hb <13 g/dL, n (%)	
yes	16 (69.6%)
no	7 (30.4%)
Hemoglobin at discharge (t3)	
(g/dL), median [IQR]	10.43 (8.9;11.2)

Hb <13 g/dL, n (%)	
yes	22 (100.0%)
no	0 (0.0%)
Hospital training, n (%)	
yes	8 (34.8%)
no	15 (65.2%)
Type of surgey, n (%)	
radical cystectomy	23 (100.0%)
laparoscopic	1 (4.3%)
robotic (Da Vinci)	22 (95.7%)
Intraoperative blood loss, n (%)	
<1000 mL	22 (95.7%)
>1000 mL	1 (6.2%)
Transfusion, n (%)	
yes	2 (8.7%)
no	21 (91.3%)

Table 3 - Demographic characteristics of the studied population.

To facilitate data analysis, it was necessary to define 5 timepoints to which we will refer:

- Time 0, t0, is the moment when patients were elected to major cystectomy surgery following cancer diagnosis;
- the time point referred to as t1 represents the moment immediately preceding the start of the prehabilitation process, this baseline status reflects the patients' condition before surgery, without any correction of hemoglobin deficiency and with their overall fitness deteriorated by the disease;
- Time 2 (t2) is defined as the point at which the prehabilitation program is completed, and blood samples are taken again for patient follow-up. At t1, the status of patients is described as they approach the time of surgery;
- discharge time is referred to as Time 3 (t3).
- Time 4, or t4, is defined as the moment 90 days after the surgical operation.

6.2 Hemoglobin trend

6.2.1 Case group

In the following graph (Figure 17), the Hb values at the time of surgery and at discharge for each patient who participated in the prehabilitation program can be observed. As shown in Table 6.1, for the cases, the average Hb at the beginning of the prehabilitation program (t1) is 11.38 g/dL, at the time of surgery (t2) it is 12.1 g/dL, and at discharge (t3) it is 10.4 g/dL. The average ΔHb is 1.7 g/dL.

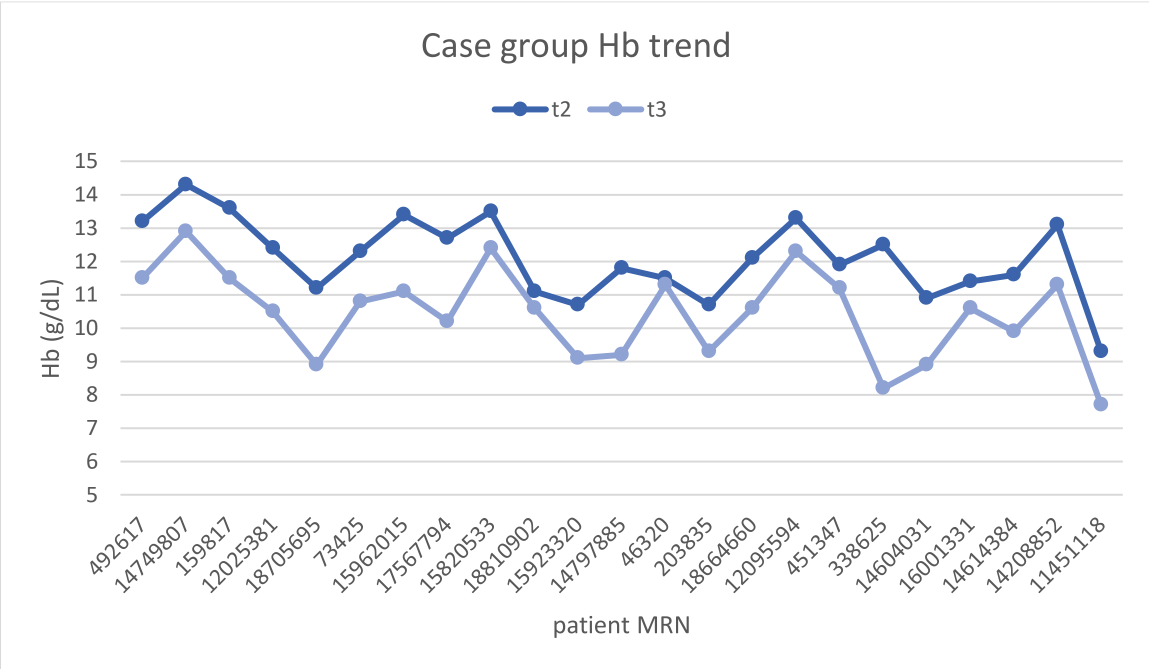

Figure 17 - Hemoglobin trend in case group both before surgery (t2) and at discharge (t3). Abbreviations: Hb= hemoglobin; MRN= medical record number.

6.2.2 Control group

For the control group, only hemoglobin values are available, as the evaluation of functional capacity is not currently adopted in clinical practice, and the data were retrieved from the 2023 cystectomy list archive. In this case, it was possible to obtain Hb values only at two time points: before surgery, i.e., at t1, and at discharge, i.e., at t2. The collected data are shown in Table 4.

n°	MR number	Surgery date	Pre-surgery Hb	Hb at discharge	Δ Hb (g/dL)	Length of stay (days)
1	346729	13/1/2023	12,8 g/dL	9,9 g/dL	2,9	32
2	603509	27/1/2023	13,8 g/dL	11,2 g/dL	2,6	10
3	11494785	2/2/2023	13,5 g/dL	11,3 g/dL	2,2	8
4	271540	23/2/2023	13,4 g/dL	10,1 g/dL	3,3	22
5	15838970	14/3/2023	13,3 g/dL	10,6 g/dL	2,7	8

6	15159795	28/3/2023	12,7 g/dL	11,6 g/dL	1,1	10
7	51725	11/4/2023	11,1 g/dL	9,3 g/dL	1,8	52
8	10800477	26/4/2023	10,6 g/dL	8,5 g/dL	2,1	9
9	242628	10/5/2023	14,3 g/dL	12,2 g/dL	2,1	17
10	15887038	23/5/2023	13,9 g/dL	12,3 g/dL	1,6	7
11	14646143	14/6/2023	10,6 g/dL	9,4 g/dL	1,2	30
12	15934387	11/7/2023	9,7 g/dL	8,1 g/dL	1,6	21
13	145246	26/7/2023	10,3 g/dL	7,8 g/dL	2,5	8
14	20402707	25/8/2023	11,4 g/dL	8,6 g/dL	2,8	8
15	13844774	12/9/2023	11,2 g/dL	9,9 g/dL	1,3	9
16	15374077	24/10/2023	11,9 g/dL	10,2 g/dL	1,7	11
17	15848782	6/10/2023	8,5 g/dL	7,2 g/dL	1,3	9
18	35873	15/11/2023	10 g/dL	7,2 g/dL	2,8	14
19	12916111	22/11/2023	12,5 g/dL	10,9 g/dL	1,6	10
20	214260	28/11/2023	14,3 g/dL	11,4 g/dL	2,9	8
21	15996646	1/12/2023	14,3 g/dL	9,8 g/dL	4,5	14
22	15945209	12/12/2023	11,6 g/dL	10,2 g/dL	1,4	7
23	15828604	15/12/2023	11,3 g/dL	9,1 g/dL	2,2	7

Table 4 – Control group demographics and Hb data. Abbreviations: Hb= hemoglobin; MR= medical record.

In the control group, the average length of stay was 14.39 days. Regarding Hb levels at t2, the average was 11.42 g/dL, while the average at discharge (t3) was 9.54 g/dL. The average ΔHb was 1.9 g/dL. Figure 18 below shows the difference in distribution for the control group between Hb values at t1 and t2.

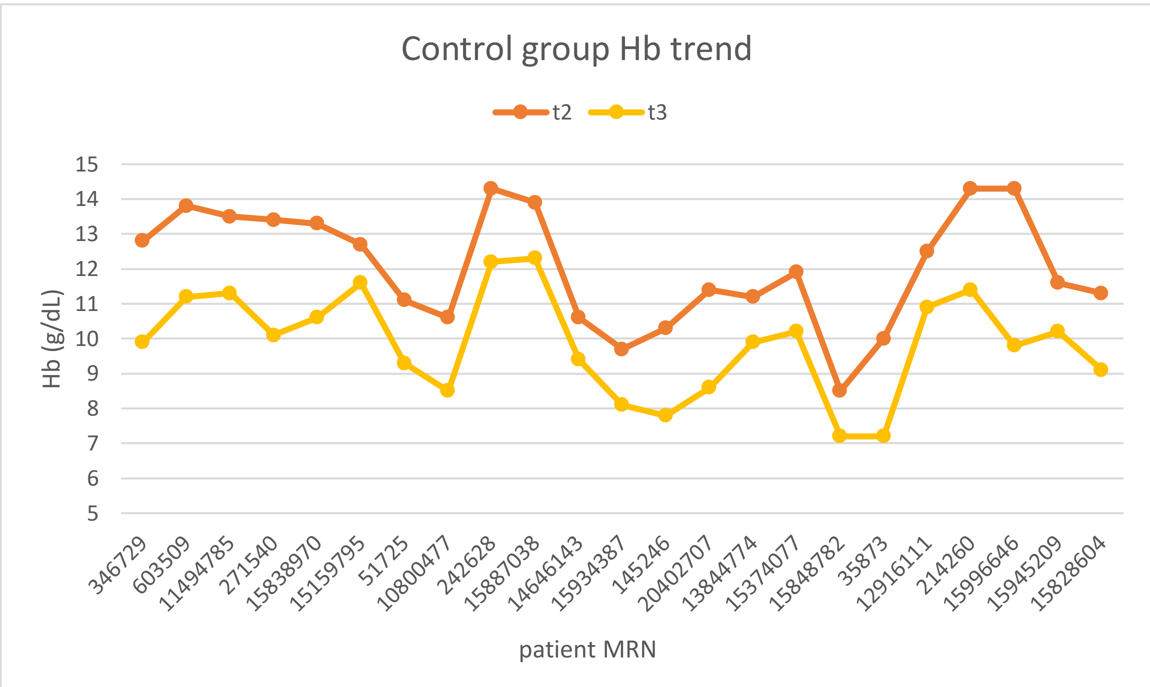

Figure 18 - Hemoglobin trend in control group both before surgery (t2) and at discharge (t3). Abbreviations: Hb= hemoglobin; MRN= medical record number.

6.2.3 Case-control comparison

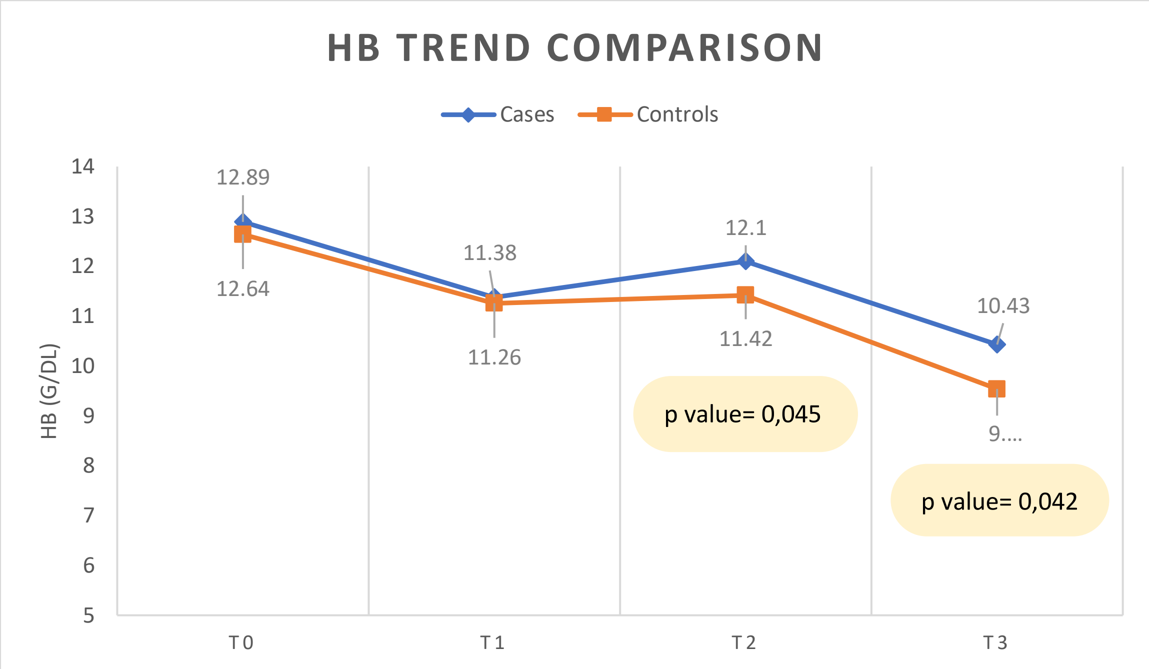

Figure 19 - Trend comparison between cases and controls.

Figure 19 shows the trend of hemoglobin levels in cases and controls at four different time points: t0, which represents the baseline, the moment when the patients were candidates for radical cystectomy and placed on the waiting list; t1, which coincides with the start of prehabilitation (cases) ore the end of chemotherapy cycles (controls); t2, the time of surgery; and t4, discharge.

It is noteworthy that no significant difference emerged at t0 and t1 regarding anemic status, while a p-value of 0.045 and another of 0.042 indicate a significant influence of prehabilitation on the hemoglobin status of the cases.

6.2.4 Anemic vs non-anemic population

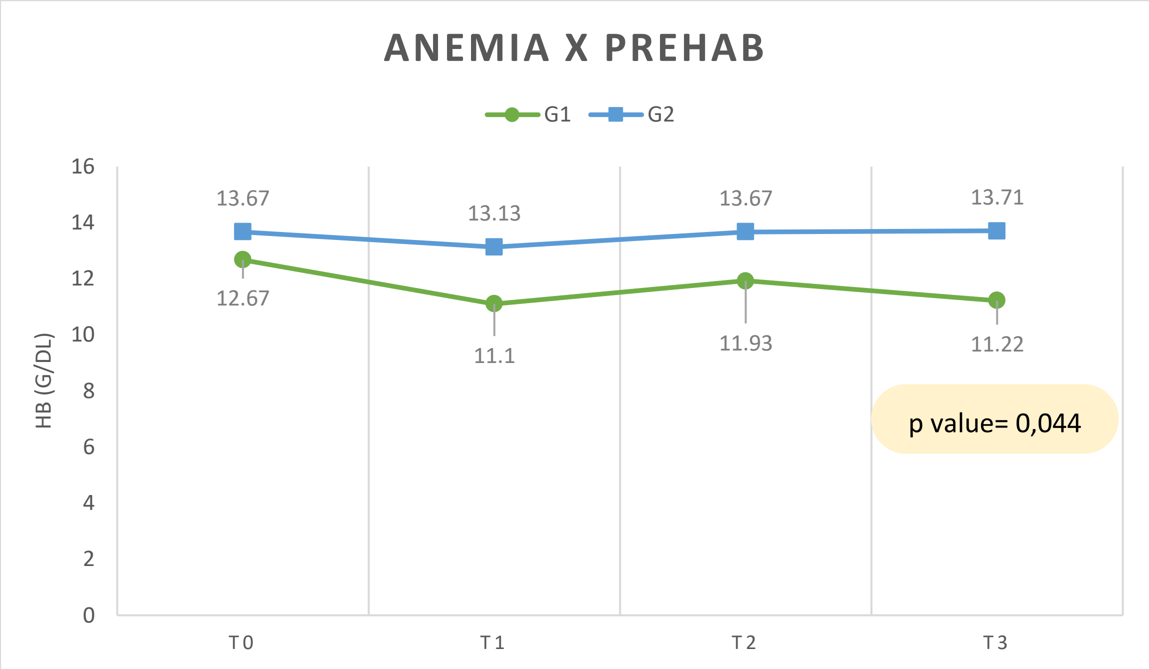

Figure 20 - Hemoglobin trend in G1 and G2 through preHAB. Abbreviations: G1= Group1 (anemic at baseline); G2= Group2 (non-anemic at baseline).

The cases were then divided into two groups: Group 1 (G1), consisting of all subjects with Hb <13 g/dL at the start of the prehabilitation program, and a second group (G2), with all patients who had higher levels. The trend of Hb levels throughout the program until discharge was analyzed for both groups. In Figure 20, the averages at the different time points are shown, highlighting the significant difference between G1 and G2 at t4 (p-value = 0.044). The mean Hb level in the case population is 13,67 g/dL while in the control group is 12,67 g/dL.

Postoperative complications are the final endpoint of this study. Figure 21 shows the percentage of patients who experienced complications in the two groups, G1 and G2. It is noteworthy that almost all complications occurred in G1 patients, i.e., those with Hb <13 g/dL at t1. Despite the higher prevalence of complications in G1, it is not possible to establish a significant relationship between anemic status at t0 and the development of complications (p-value = 0.9). Figure 22 shows the distributions of the main complications that occurred in the two groups.

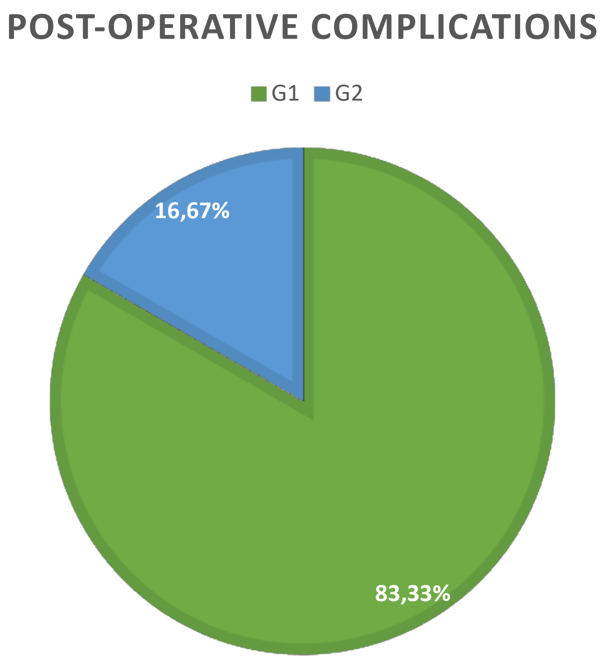

Figure 21 – Post-operative complications rate by anemia.

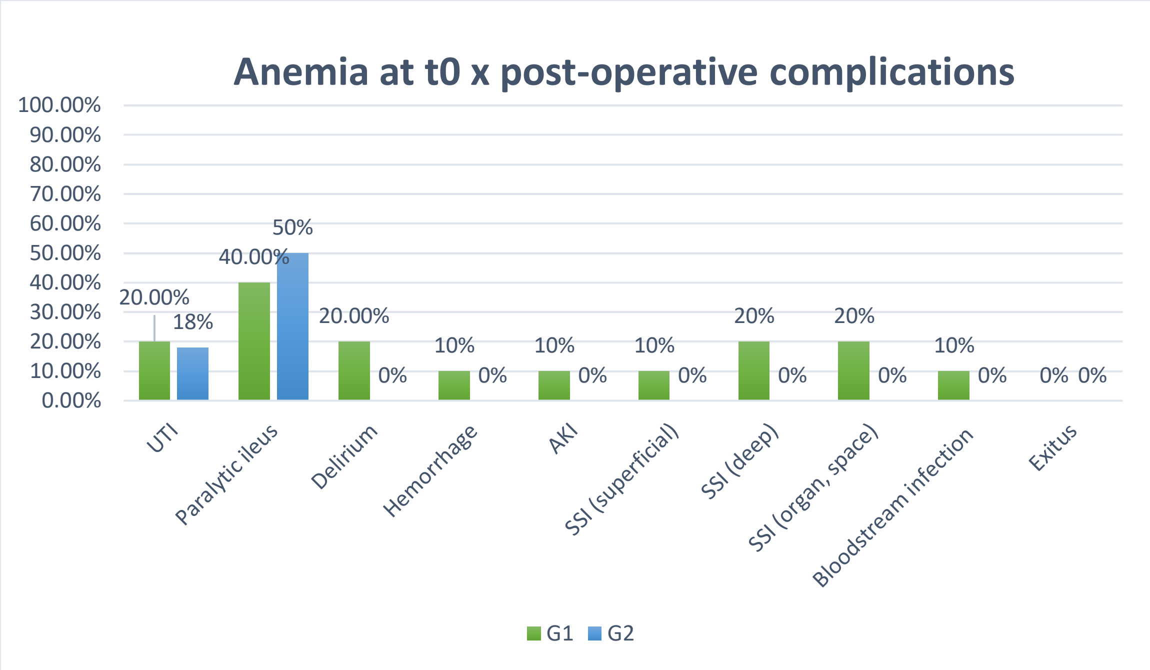

Figure 22 – Post-operative complications rate by anemia.

6.3 Descriptive by anemia before prehabilitation

Before presenting these results, an important clarification is necessary: this study is a pilot trial and represents the initial data collection of a larger project, both in terms of duration and sample size. The total number of patients recruited is relatively small, which presents a limitation and necessitates the use of specific data analysis methods. Inferential statistics typically consider the hypothesis valid when p-values are <0.05. However, in this study, given the small sample size of only 23 patients, it was necessary to expand this significance threshold. The risk is that some statistically significant results may actually stem from inherent biases within the study itself. Therefore, only data with a p-value ≤0.150 were considered.

This analysis was conducted by defining two groups to compare their outcomes: Group 1 (G1) includes patients who were anemic at t0, with hemoglobin levels <13 g/dL, while Group 2 (G2) consists of those who did not present anemia.

Table 5 - Demographic characteristics by anemia at t0.

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
Gender, n (%)				0.366
female	7 (30.4%)	6 (37.5%)	1 (14.3%)	
male	16 (69.6%)	10 (62.5%)	6 (85.7%)	
Charlson, median	3.0 [2.0 ; 3.5]	3.0 [2.0 ; 4.0]	2.0 [2.0 ; 2.0]	0.021
Charlson grade, n (%)				0.727
mild	6 (54.50%)	3 (42.9%)	3 (75.00%)	
moderate	3 (27.30%)	2 (28.6%)	1 (25.00%)	
severe	2 (18.20%)	2 (28.6%)	0 (0.0%)	
Length of hospital stay, (days) median	9.0 [7.0;14.0]	9.5 [6.0;14.0]	9.0 [7.0;13.5]	0.564

Table 5 illustrates the distribution of sex, comorbidity score, and length of hospital stay in the study population. The gender distribution among anemic subjects (data presented in Table 3) reveals that 37.5% were women and 62.5% were men. In absolute numbers, this corresponds to 6 women out of 7 and 10 men out of 16.
The Charlson comorbidity score, used to assess comorbidities, averaged 3.0, with a higher score in G1 (3.0) compared to G2 (2.0). In this case, the p-value indicates a significant relationship between anemic status at t0 and the score difference between the two groups.
The average length of hospital stay was 9 days, ranging from a minimum of 7 days to a maximum of 14. When analyzing this data in relation to anemia levels at t0, we observe that G1 had an average hospital stay of 0.5 days longer than G2.

6.3.1 Functional capacity before prehabilitation x anemia at t0

The data presented in the following paragraph were obtained by correlating the variable 'anemia at t0' with variables related to functional capacity. The patients' residual functional capacity at the start of prehabilitation (t0) was assessed based on the results of several tests, including the 6-minute walk test (6MWT), handgrip strength, maximal inspiratory pressure (MIP), and the Short Physical Performance Battery (SPPB). This allowed us to divide the group into two categories: frail patients (n=8), who were monitored in a facility for their training, and pre-frail patients (n=15), who trained at home, as shown in Table 6. Below in the same table, there is an overview of the functional capacity at t0.
As can be observed, even before prehabilitation began, a difference was evident between anemic and non-anemic patients. Both the 6MWT (p-value = 0.052) and the IPAQ questionnaire (p-value = 0.072) highlight a gap between the two patient groups, with more favorable results for the non-anemic group. Additional confirmation comes from the distribution of data for the MIP variable, with a p-value of 0.122.

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
6MWT (m), median	457.5 [379.5;531.8]	430.0 [366.5;540.0]	468.0 [457.5;512.5]	0.192
(%), median	100.0	90.5	103.0	0.052
Dominant handgrip strength (kg), median	31.0 [25.6;40.5]	30.0 [23.2;40.0]	38.0 [28.5;40.5]	0.403
MIP (cmH_2O), median	79.5	54.0	92.0	0.122
IPAQ, n (%)				0.072
Low	7 (30.4%)	7 (43.8%)	0 (0.0%)	
Moderate	15 (65.2%)	8 (50.0%)	7 (100.0%)	
High	1 (4.3%)	1 (6.2%)	0 (0.0%)	
SPPB score, median	10.5	9.0	11.0	0.613
Age at admission, median	71.5 [64.6 ; 76.2]	71.5 [64.9 ; 75.1]	71.0 [66.4 ; 75.2]	0.947
Frailty, n (%)				0.272
yes	8 (34.78%)	8 (50.0%)	0 (0.0%)	
no	15 (65.22%)	8 (50.0%)	7 (100.0%)	

Table 6 - Functional capacity before prehabilitation (t0). The 6MWT result can be described as a percentage greater than 100% because it is calculated upon the expected distance for healthy patients. Abbreviations: 6MWT= 6 minutes walking test; MIP= maximum inspiratory pressure; IPAQ= International Physical Activity Questionnaire.

Regarding how insufficient Hb levels influenced the training plan, the results are shown in Table 7. It should be noted that hospital-based training was reserved for patients classified as frail.

It is evident that for all non-anemic patients, independent training was deemed sufficient, without the need for a personalized program provided by the hospital. The dynamic was different for anemic patients: 50% were classified as pre-frail, while the remaining 50% underwent a supervised training program. The p-value of 0.052 indicates a significant relationship between assignment to hospital-based training and the presence of anemia.

For further details, refer to Chapter 6, Section 4.1.

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
Hospital training, n (%)				0.052
yes	8 (34.78%)	8 (50.0%)	0 (0.0%)	
no	15 (65.22%)	8 (50.0%)	7 (100.0%)	

Table 7 - Hospital training by anemia at t0.

6.3.2 Anemia at the end of the preHAB x anemia at t0

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
Hemoglobin (g/dL) at t1, median	11.3 [10.6 ; 13.1]	11.2 [10.8 ; 12.3]	14.2 [10.5 ; 14.8]	0.300
Hb <13g/dL, n (%)				0.137
yes	16 (69.6%)	13 (81.2%)	3 (42.9%)	
no	7 (30.4%)	3 (18.8%)	4 (57.1%)	

Table 8 - How anemia at the beginning of the preHAB links with anemia at the end. T1, or time 1 described as the end of the prehabilitation, is the timepoint took into analysis.

Table 8 presents data concerning anemia, specifically the relationship between low Hb levels at baseline (t0) and their influence on anemic status at t1.

The distribution of anemia within the patient sample remains unchanged, with 16 patients (69.9%) still presenting anemia, while 7 patients (30.4%) have adequate Hb levels (refer to Table 6.1 for comparison with t0).

Of the 16 anemic patients at t0, 13 (81.2%) remain anemic, while 3 (18.8%) have improved. Among the 7 non-anemic patients, 4 (57.1%) maintained sufficient hemoglobin status, while 3 (42.9%) experienced deterioration, developing anemia by t1. This worsening is likely attributable to the oncological condition and the adverse effects of chemotherapy.

The p-value suggests that there is no significant influence of Hb levels at t0 on Hb levels at t1 (p-value = 0.300). However, the values in the table indicate a significant relationship (p-value = 0.137) between the distribution of anemia at t1 among previously anemic patients and their anemic status at t1.

6.3.3 PreHAB x anemia at t0

Within the analyzed patient cohort, 77.3% (n=17) of the patients completed the 4-week prehabilitation program, while 22.7% discontinued the program (Table 9). This resulted in an average treatment duration of 3 weeks, with a difference of 0.5 weeks longer for Group 1.

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
preHAB status, n (%)				0.135
completed	17 (77.3%)	10 (66.7%)	7 (100.0%)	
interrupted	5 (22.7%)	5 (33.3%)	0 (0.0%)	
preHAB length (weeks), median	3.0 [3.0;4.0]	3.0 [3.0;4.0]	4.0 [3.5;4.5]	0.134

Table 9 - preHAB compliance by anemia at t0.

A p-value of 0.135 supports the hypothesis that initial anemic status influences adherence to the prehabilitation program: 100% of patients who were not originally anemic completed the program.

6.3.4 Anemia at discharge x anemia at t0

Table 10 shows that at t2, nearly all patients exhibit anemia, with a percentage of approximately 95.7% (22 patients). The average hemoglobin levels are 9.4 g/dL, with a slight difference of 0.2 g/dL between G1 and G2.

	Total	**G1**	**G2**	**p value**
	N= 23	N= 16	N= 7	
Intraoperative blood loss, n (%)				1.000
<1000 mL	22 (95.7%)	15 (93.8%)	7 (100.0%)	
>1000 mL	1 (6.2%)	1 (4.3%)	0 (0.0%)	
Transfusion, n (%)				1.000
yes	2 (8.7%)	2 (12.5%)	0 (0.0%)	
no	21 (91.3%)	14 (87.5%)	7 (100.0%)	
Hemoglobin (g/dL), median	9.4 [8.9 ; 11.2]	9.4	9.6	
Hb <13 d/dL, n (%)				
yes	22 (95.7%)	16 (100.0%)	6 (85.71%)	
no	1 (6.2%)	0 (0.0%)	1 (14.29%)	

Table 10 - Surgery data by anemia at t0.

All patients underwent radical cystectomy, with 95.7% benefiting from robotic surgery using the Da Vinci system, while one patient (4.3%) underwent a laparoscopic approach due to complications that could not be resolved robotically (Table 3). The patient referenced in Table 3 for intraoperative bleeding greater than 1000 mL is the same patient who had the surgical approach changed.
A high p-value for the data in Table 10 excludes a significant relationship between the variables.

6.3.5 Postoperative complications x anemia at t0

	Total	G1	G2	p value
	N= 23	N= 16	N= 7	
Hospital readmission, n (%)				1.000
yes	5 (21.7%)	4 (25.0%)	1 (14.3%)	
no	18 (78.3%)	12 (75.0%)	6 (85.7%)	
Re-do interventions; n (%)				1.000
yes	1 (4.3%)	1 (6.2%)	0 (0.0%)	
no	22 (95.7%)	15 (93.8%))	7 (100.0%)	
Post-operative complications, n (%)				0.193
yes	12 (52.20%)	10 (83.33%)	2 (16.67%)	
no	11 (47.80%)	6 (54.54%)	5 (45.46%)	

Table 11 - Postoperative course up to 90 days.

T3 is the timeframe evaluated in this paragraph.
As shown in Table 11, a second hospitalization occurred in 21.7% of the studied population, with a slightly higher prevalence in patients from G1. However, no significant relationship was observed between anemia status at t0 and surgical outcomes (p-value = 1.000).
Surgical reintervention was necessary in only one case, a patient from G1, due to failure of the initial procedure.
Regarding complications, they occurred in 52.20% of cases, with a p-value of 0.193, which rejects the hypothesis of a correlation with the presence of anemia at t0. Nonetheless, the limitations of the studied sample should be considered, which does not allow for a definitive exclusion of the relationship between anemia and the rate of postoperative complications.

	Total	G1	G2	P value
	N= 12	N= 10	N= 2	
Complications type, n (%)				
Acute kidney injury (AKI)				1.000
yes	1 (8.3%)	1 (10.0%)	0 (0.0%)	
no	11 (91.7%)	9 (90.0%)	2 (100.0%)	
Acute respiratory distress sdr.				1.000
yes	1 (8.3%)	1 (10.0%)	0 (0.0%)	
no	11 (91.7%)	9 (90.0%)	2 (100.0%)	
Pneumonia				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	10 (100.0%)	2 (100.0%)	
Cardiac arrest				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	10 (100.0%)	2 (100.0%)	
Arrhytmia				.

yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	10 (100.0%)	2 (100.0%)	
Deep venous thrombosis				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	10 (100.0%)	2 (100.0%)	
SSI (superficial)				1.000
yes	1 (8.3%)	1 (10.0%)	0 (0.0%)	
no	11 (91.7%)	9 (90.0%)	2 (100.0%)	
SSI (deep)				1.000
yes	2 (16.7%)	2 (20.0%)	0 (0.0%)	
no	10 (83.3%)	6 (80.0%)	2 (100.0%)	
SSI (organ, space)				1.000
yes	2 (16.7%)	2 (20.0%)	0 (0.0%)	
no	10 (83.3%)	8 (80.0%)	2 (100.0%)	
Bloodstream infection				1.000
yes	1 (8.3%)	1 (10.0%)	0 (0.0%)	
no	11 (91.7%)	9 (90.0%)	2 (100.0%)	
Urinary tract infection (UTI)				0.091
yes	4 (33.3%)	2 (20.0%)	2 (100.0%)	
no	9 (66.7%)	8 (90.0%)	0 (0.0%)	
Paralytic ileus				1.000
yes	5 (41.7%)	4 (40.0%)	1 (50.0%)	
no	7 (58.3%)	6 (60.0%)	1 (50.0%)	
Delirium				.
yes	2 (16.7%)	2 (20.0%)	0 (0.0%)	
no	10 (83.3%)	8 (80.0%)	7 (100.0%)	
Hemorrhage				.
yes	1 (8.3%)	1 (10.0%)	0 (0.0%)	
no	11 (91.7%)	9 (90.0%)	2 (100.0%)	
Exitus				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	10 (100.0%)	2 (100.0%)	

Table 12 - Complications up to 90 days by anemia at t0. Abbreviations: SSI= surgical site infection.

The complications listed in Table 12 were assessed at what we can define as time 3, which covers the period up to 90 days post-surgery. The main postoperative complications evaluated and included in the study are as follows:

- Acute kidney injury: 1 case, representing a prevalence of 8.3%, occurring in Group 1.
- Acute respiratory distress syndrome: 1 case, representing a prevalence of 8.3%, occurring in Group 1.
- Pneumonia: Not detected.
- Cardiac arrest: Not detected.
- Arrhythmias: Not detected.
- Deep vein thrombosis (DVT): Not detected.
- Superficial surgical site infection: 1 case, with a prevalence of 8.3%, occurring in Group 1.

- Deep tissue infections at the surgical site: 2 cases, with a prevalence of 16.7%, both in Group 1.
- Deep infections at the surgical site, defined as organ or contiguous space infections: 2 cases, with a prevalence of 16.7%, both in Group 1.
- Septicemia/sepsis: 1 case, with a prevalence of 8.3%, occurring in Group 1.
- Urinary tract infection (UTI): 4 cases, with a prevalence of 33.3%, including 2 cases in Group 1 and 2 in Group 2; a significant relationship is noted with a p-value of 0.091 relative to anemia status at t0.
- Paralytic ileus: 5 cases, with a prevalence of 41.7%, including 4 cases in Group 1 and 1 in Group 2.
- Delirium: 2 cases, with a prevalence of 16.7%, occurring in Group 1.
- Hemorrhage: 1 case, with a prevalence of 8.3%, occurring in Group 1.
- Death: Not detected.

It should be noted that it was not possible to calculate the p-value for all variables.
Complications were collected not only by type but also by severity. The Clavien-Dindo score was used, and the results are listed below in Table 13. As shown, most complications were of mild severity with a score between 1 and 2: 83.33%, with 10 out of 12 cases being grade 2 complications, which include those requiring blood transfusions.

	Total	**G1**	**G2**	**p value**
	N= 12	N= 10	N= 2	
Clavien-Dindo, n (%)				1.000
1	1 (7.7%)	1 (10.0%)	0 (0.0%)	
2	10 (83.33%)	8 (80.0%)	2 (100.0%)	
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3a	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3b	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4a	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4b	1 (7.7%)	1 (10.0%)	0 (0.0%)	
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Table 13 - Complications grade by the Clavien-Dindo classification by anemia at t0.

6.4 Descriptive by anemia at the end of the prehabilitation

We are now focusing on a different timepoint which is the time 1, that is the moment at the end of the 4-weeks prehabilitation program. New blood samples were collected for every patient that went through the preHAB. New physical measurements were also collected.
The next paragraphs report the data related with the anemic status at t1 to see if there is any proof that low hemoglobin levels can affect a patient's fitness.

6.4.1 anemia before the preHAB x anemia at t1

	Total	G1	G2	p value
	N=23	**N=16**	**N=7**	
Hemoglobin (g/dL), median [IQR]	11.9 [10.8;13.7]	11.3 [10.5;12.4]	13.8 [12.4;15.0]	0.061

Table 14 - Anemia before preHAB (t0) by anemia at t1.

Table 14 displays the hemoglobin values collected during the sampling at the beginning of prehabilitation (t0). It is evident that G1, which presents with anemia at t0, has an average hemoglobin level 1.7 g/dL lower than the recommended cutoff of 13 g/dL. G2, composed of the non-anemic portion of the population, has an average value of 13.8 g/dL. A p-value of 0.061 supports the hypothesis that anemia at t1 is related to the presence of anemia at t0, as one would expect.

6.4.2 Functional capacity at t1 x anemia at t1

	Total	**G1**	**G2**	**p value**
	N= 8	N= 4	N= 4	
6MWT (m), median [IQR]	406.0 [372.0;440.0]	372.0 [355.0;389.0]	474.0 [474.0;474.0]	0.221
(%), median [IQR]	91.0 [89.5;96.5]	95.0 [91.5;98.5]	91.0 [91.0;91.0]	1.000
Dominant handgrip strength (kg), median	33.0 [27.5;96.5]	28.0 [25.0;31.0]	33.0 [33.0;33.0]	
IPAQ, n (%)				0.333
Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Moderate	4 (50.0%)	3 (75.0%)	1 (25.0%)	
High	4 (50.0%)	1 (25.0%)	3 (75.0%)	
SPPB score, median	9.0 [9.0;10.5]	9.0 [9.0;9.0]	12.0 [12.0;12.0]	0.157

Table 15 - Functional capacity at the end of the preHAB (t1) by anemia at t1. The 6MWT result can be described as a percentage greater than 100% because it is calculated upon the expected distance for healthy patients. Abbreviations: 6MWT= 6 minutes walking test; MIP= maximum inspiratory pressure; IPAQ= International Physical Activity Questionnaire.

Table 15 describes the fitness levels and the main differences between G1 and G2 at t1. The three variables examined show higher and thus better values for G2, indicating superior physical fitness in the non-anemic group.

6.4.5 Anemia at discharge x anemia at t1

	Total	G1	G2	P value
	N= 23	N= 16	N= 7	
Hemoglobin (g/dL), median	9.4 [8.9 ; 11.2]	9.6 [8.9;11.0]	9.4 [1.0;11]	0.916

Tablev16 – Hb levels at discharge (t3) by anemia at t1.

Table 16 shows the hemoglobin levels at discharge. It can be observed that, despite widespread anemia across the population, the hemoglobin values for G1 and G2 differ by only 0.2 g/dL. No significant relationship is found between anemia at t3 and t1, given the p-value. However, it is worth noting that the difference between G1 and G2 is minimal, in contrast to the differences observed in earlier stages of the program: whereas at t0 the difference between G1 and G2 was 2.5 g/dL (G1 = 11.3 g/dL, G2 = 13.8 g/dL; see Table 7.1), it is now 87.5% less.

6.4.6 Postoperative complications x anemia at t1

	Total	G1	G2	P value
	N= 23	N= 16	N= 7	
Hospital readmission, n (%)				1.000
yes	5 (21.7%)	4 (25.0%)	1 (14.3%)	
no	18 (78.3%)	12 (75.0%)	6 (85.7%)	
Re-do interventions; n (%)				1.000
yes	1 (4.3%)	1 (6.2%)	0 (0.0%)	
no	22 (95.7%)	15 (93.8%)	7 (100.0%)	
Post-operative complications, n (%)				0.193
yes	12 (52.2%)	8 (50.0%)	4 (57.1%)	
no	11 (47.8%)	8 (50.0%)	3 (42.9%)	

Table 17 - Postoperative course up to 90 days.

The considerations we can make regarding the relationship between anemia at t1 and the postoperative course are similar to those observed in section 6.2.5. The only difference is in the distribution of complications: it is noted that 50% of patients in G1 with anemia at t1 experienced complications 90 days post-surgery, whereas in G1 with anemia at t0, 62.45% experienced complications.

	Total	G1	G2	P value
	N= 12	N= 8	N= 4	
Complications type, n (%)				
Acute kidney injury (AKI)				1.000
yes	1 (8.3%)	1 (12.5%)	0 (0.0%)	
no	11 (91.7%)	7 (87.5%)	4 (100.0%)	
Acute respiratory distress sydr.				1.000
yes	1 (8.3%)	1 (12.5%)	0 (0.0%)	
no	11 (91.7%)	7 (87.5%)	4 (100.0%)	
Pneumonia				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	8 (100.0%)	4 (100.0%)	
Cardiac arrest				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	8 (100.0%)	4 (100.0%)	
Arrhytmia				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	8 (100.0%)	4 (100.0%)	
Deep venous thrombosis				.
yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	8 (100.0%)	4 (100.0%)	
Bloodstream infection				1.000
yes	1 (8.3%)	2 (14.28%)	0 (0.0%)	
no	11 (91.7%)	14 (85.72%)	7 (100.0%)	
SSI (superficial)				1.000
yes	1 (8.3%)	1 (12.5%)	0 (0.0%)	
no	11 (91.7%)	7 (87.5%)	4 (100.0%)	
SSI (deep)				0.515
yes	2 (16.7%)	2 (25.0%)	0 (0.0%)	
no	10 (83.3%)	6 (75.0%)	4 (100.0%)	
SSI (organ, space)				0.515
yes	2 (16.7%)	2 (25.0%)	0 (0.0%)	
no	10 (83.3%)	6 (75.0%)	4 (100.0%)	
Urinary tract infection (UTI)				0.091
yes	4 (33.3%)	1 (12.5%)	3 (75.0%)	
no	8 (66.7%)	7 (87.5%)	1 (25.0%)	
Paralytic ileus				1.000
yes	5 (41.7%)	3 (37.5%)	2 (50.0%)	
no	7 (58.3%)	5 (62.5%)	2 (50.0%)	
Delirium				.
yes	2 (16.7%)	2 (25.0%)	0 (0.0%)	
no	10 (83.3%)	6 (75.0%)	4 (100.0%)	
Hemorrhagia				.
yes	1 (8.3%)	1 (12.5%)	0 (0.0%)	
no	11 (91.7%)	7 (87.5%)	4 (100.0%)	
Exitus				.

yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
no	12 (100%)	8 (100.0%)	4 (100.0%)	

Table 18 – Complications up to 90 days by anemia at t1. Abbreviations: SSI= surgical site infection.

	Total	**G1**	**G2**	**p value**
	N= 12	N= 10	N= 2	
Clavien-Dindo, n (%)				1.000
1	1 (7.7%)	1 (10.0%)	0 (0.0%)	
2	10 (83.33%)	8 (80.0%)	2 (100.0%)	
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3a	0 (0.0%)	0 (0.0%)	0 (0.0%)	
3b	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4a	0 (0.0%)	0 (0.0%)	0 (0.0%)	
4b	1 (7.7%)	1 (10.0%)	0 (0.0%)	
5	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Table 19 - Complications grade by the Clavien-Dindo classification by anemia at t1.

6.5 Functional capacity trend

6.5.1 Before prehabilitation

Tests	Total
	N= 23
6MWT (m), median [IQR]	457.5 [379.5;531.8]
6MWT (%), median [IQR]	100.0 [85.0;109.0]
Dominant handgrip strength (kg), median [IQR]	31.0 [25.6;40.5]
Dominant handgrip strength (%), median [IQR]	107.5 [96.2;126.0]
Nondominant handgrip strength (kg), median [IQR]	30.0 [25.0;38.0]
Nondominant handgrip strength (%), median [IQR]	109.4 [97.0;131.5]
Spirometry: MIP (cmH_2O), median [IQR]	79.5 [41.0;95.5]
IPAQ, n (%)	
Low	7 (30.4%)
Moderate	15 (65.2%)
High	1 (4.4%)
SPPB total score, median [IQR]	10.5 [9.0;12.0]
SPPB subtest 1 score, median [IQR]	4.0 [3.2;4.0]
SPPB subtest 2 score, median [IQR]	4.0 [4.0;4.0]
SPPB subtest 3 score, median [IQR]	3.0 [2.0;4.0]
Fragility, n (%)	
Yes	5 (21.7%)
No	18 (78.3%)

Table 20 – Functional capacity measurements before preHAB (t0). Abbreviations: MIP=Maximal Inspiratory Pressure; IPAQ= International Physical Activity Questionnaire; SPPB=Short Physical Performance Battery.

Table 20 lists all the measurements collected during the physical assessment of patients at the beginning of the prehabilitation program.
The 6-Minute Walk Test (6MWT) had an average of 457.5 meters, which corresponds to 100% of the expected value normalized for age. The average is not low, with a minimum percentage value of 85%, indicating a population with generally good functional reserve.
It should be noted that the reference target values for this test depend on sex and age, and are estimated using the following formulas:

$$Women = 867 - (5{,}71 * age) + (1{,}03 * height)$$
$$Men = 525 - (2{,}86 * age) + (2{,}71 * height) - BMI$$

The reference values for the age group analyzed are thus: 439m-571m for women and 498m-622m for men.

However, it is necessary to evaluate the population in its differences rather than as a whole. The main difference to consider is the presence or absence of anemia at baseline (t0).
In Table 6 of the previous chapter, the same data were reported in relation to the presence or absence of anemia. It is noted that patients in G1 (anemic at t0) have an average distance walked of 430m in 6 minutes (equivalent to 90.5% of the expected value), which is below the expected value for both men and women. In contrast, G2 (non-anemic) had an average of 468m, equal to 103.0%. The p-value for this comparison is 0.052 (Table 6).
The dominant hand grip strength shows less significant variation, with the average being 31kg (Table 8.1), equivalent to 107.5% of the expected value. The difference between the two groups, G1 and G2, is 8kg, where the maximum value in G1 is the minimum value in G2 (Table 6).
Regarding spirometry, the Maximum Inspiratory Pressure (MIP) is described by an average value of 79.5 cmH_2O. Analyzing the distribution in the two groups, G1 and G2, the trend is reversed: G1 has, on average, higher values.
For the IPAQ, since it is not a continuous variable, we do not have an average value. However, we observe that only 30.4% of the population was categorized as low activity. The remaining 69.6% is moderately or very active. Looking more closely (Table 6), we see that 100% of G2 is moderately active, while in G1, 43.8% are considered inactive in their daily life.
The Short Physical Performance Battery (SPPB) at t0 has an average score of 10.5, with a range between 9.0 and 12.0, which does not suggest a fragile population. Referring to the distribution based on anemia status (Table 6), despite the good average, there are significant differences between G1 and G2. In G1, the score range is from 8.5 to 12.0, with an average of 9.0: this delineates a subset within G1 with scores <9, which can be defined as having mild frailty. This trend is not present in G2, where all values are >10 (frailty cut-off ≤9).
Frailty was thus detected in 8 patients out of 23, all of whom belong to G2.

6.5.2 At end prehabilitation

Tests	Total
	N= 8
6MWT (m), Median [IQR]	406.0 [372.0;440.0]
6MWT (%), Median [IQR]	91.0 [89.5;96.5]
Dominant handgrip strength (kg), Median [IQR]	33.0 [27.5;33.5]
Dominant handgrip strength (%), Median [IQR]	155.0 [140.0;170.0]
Nondominant handgrip strength kg), Median [IQR]	31.0 [26.5;31.5]
Nondominant handgrip strength (%), Median [IQR]	160.0 [148.5;171.5]
Spirometry MIP (cmH_2O), Median [IQR]	44.0 [44.0;44.0]
IPAQ, n (%)	
low	
moderate	2 (66.7%)
high	1 (33.3%)
SPPB total score, Median [IQR]	9.0 [9.0;10.5]
SPPB subtest 1 score, Median [IQR]	4.0 [4.0;4.0]
SPPB subtest 2 score, Median [IQR]	3.0 [3.0;3.5]
SPPB subtest 3 score, Median [IQR]	2.0 [2.0;3.0]
Fragility, n (%)	
Yes	2 (25.0%)
No	6 (75.0%)

Table 21 - Functional capacity measurements of the end of the preHAB (t2). Abbreviations: MIP=Maximal Inspiratory Pressure; IPAQ= International Physical Activity Questionnaire; SPPB=Short Physical Performance Battery.

It is emphasized that the sample in Table 21 consists of only 8 patients who were classified as "frail" and thus underwent training in the facility. These are the only patients for whom measurements were also taken two months after surgery.

6.5.3 Two months after prehabilitation

Tests	Total
	N= 8
6MWT (m), Median [IQR]	405.0 [381.5;420.2]
6MWT (%), Median [IQR]	79.0 [76.8;83.0]
Dominant handgrip strength (kg), Median [IQR]	20.0 [20.0;25.7]
Dominant handgrip strength (%), Median [IQR]	77.0 [77.0;77.0]
Nondominant handgrip strength (kg), Median [IQR]	22.0 [20.0;23.4]
Nondominant handgrip strength (%), Median [IQR]	76.0 [76.0;76.0]
Spirometry MIP (cmH_2O), Median [IQR]	81.0 [67.0;95.0]
IPAQ, n (%)	
low	1 (33.3%)
moderate	2 (66.7%)
high	
SPPB total score, Median [IQR]	10.0 [9.8;10.2]
SPPB subtest 1 score, Median [IQR]	4.0 [4.0;4.0]
SPPB subtest 2 score, Median [IQR]	4.0 [3.8;4.0]
SPPB subtest 3 score, Median [IQR]	2.0 [2.0;2.2]
Fragility, n (%)	
Yes	2 (25.0%)
No	6 (75.0%)

Table 22 - Functional capacity measurements 2 months after preHAB (t4). Abbreviations: MIP=Maximal Inspiratory Pressure; IPAQ= International Physical Activity Questionnaire; SPPB=Short Physical Performance Battery.

Table 22 presents the data regarding functional capacity 60 days after surgery. Only 8 patients are included in this report and they are those who were classified as "frail" and thus underwent training in the facility. These are the only patients for whom measurements were also taken at the end of the 4-week prehabilitation program.

7 Discussion

7.1 Primary endopint: Hemoglobin level comparison

Hemoglobin (Hb) is a crucial determinant of oxygen-carrying capacity, directly influencing tissue oxygenation. Surgical stress, especially in major operations, often leads to significant blood loss, which can result in perioperative anemia, impacting recovery time, increasing infection rates, and delaying wound healing. Postoperative anemia has been shown to correlate with increased risk of morbidity and mortality, therefore, maintaining adequate hemoglobin levels before, during, and after surgery is critical for reducing adverse outcomes. In the perioperative setting, particularly during major surgeries such as cystectomies, maintaining appropriate Hb levels is essential. Hemoglobin's primary role in oxygen transportation is vital in the surgical context. Inadequate tissue oxygenation during or after surgery can compromise organ function and delay healing processes. Low Hb levels or perioperative anemia result in reduced oxygen delivery to tissues, which can exacerbate cellular hypoxia, impairing the body's capacity to heal effectively postoperatively. It has been shown that maintaining sufficient oxygenation is linked to better postoperative outcomes, including shorter hospital stays and faster recovery times.

Perioperative anemia, a common occurrence due to blood loss during surgery or poor preoperative Hb levels, is associated with increased postoperative complications. These include a higher likelihood of infections, delayed wound healing, and prolonged hospitalization. Anemia can also trigger compensatory physiological responses such as tachycardia and increased cardiac output, placing additional stress on the cardiovascular system.

Recent advancements in surgical care focus on prehabilitation programs that aim to optimize a patient's physiological condition before surgery. Preoperative optimization of Hb levels, especially in patients identified as anemic, is increasingly recognized as a critical intervention. Adequate Hb levels during the recovery period are just as important. Postoperative anemia has been associated with higher risks of complications, including cardiovascular events, respiratory failure, and extended dependency on mechanical ventilation.

A 2021 study[117] published in *The Lancet* explored the relationship between perioperative hemoglobin levels and surgical outcomes, demonstrating that patients with optimized Hb preoperatively showed significant reductions in postoperative complications compared to those with lower Hb levels. Additionally, the study emphasized the importance of personalized hemoglobin management protocols in the perioperative period to enhance recovery, decrease hospital stay durations, and reduce the overall burden of healthcare resources.

By maintaining adequate hemoglobin levels, either through prehabilitation, perioperative care, or postoperative interventions, surgeons can reduce adverse outcomes, improve patient recovery, and minimize the risk of complications like infection or prolonged healing time. Hemoglobin remains a central factor in ensuring better overall surgical outcomes, particularly in patients undergoing complex procedures with high risks of blood loss, and that is why it is the primary endpoint in this study.

The control group used was retrieved from the 2023 historical database of cystectomies. It consists of 23 patients who meet the inclusion criteria of the present study, reflect the sample

under examination, but who underwent surgery prior to the start of the prehabilitation program and, therefore, could not benefit from it.
The primary endpoint was the comparison of hemoglobin levels between patients who received prehabilitation and those who did not, across four time points: baseline, end of prehabilitation/chemotherapy, surgery, and discharge. The results displayed in Figure 19 show that at baseline, the hemoglobin levels of the two groups were comparable: the average hemoglobin level at baseline was 12,77 g/dL for both cases and controls, with a small difference of 0,25 g/dL between the two. This suggests that patients were evenly matched in terms of initial health status.
The hemoglobin status was assessed similar between cases and controls even at the second timepoint, t1, which is the start of preHAB for the case group and the end of chemotherapy for the control group. It is well displayed, though, that the mean Hb level dropped significantly in both groups: the Δ Hb was 1,51 g/dL for cases and 1,38 g/dL for controls. This occurs presumably because of oncological status, chemotherapy and malnutrition.
However, by the time of surgery, a statistically significant difference in hemoglobin levels emerged, with the prehabilitation group maintaining higher hemoglobin levels with a mean Hb of 12.10 g/dL vs 11.42vg/dL in the control group (p value= 0.045). This trend continued postoperatively, where at discharge, the prehabilitation group still had significantly higher Hb levels (mean Hb 10.43vg/dL vs 9.54 g/dL in controls, p value= 0.042).
This sustained higher Hb level in the prehabilitation group indicates that iron intravenous therapy associated with prehabilitation may play a role in reducing perioperative anemia. The effect is particularly important given the link between perioperative anemia and increased postoperative complications such as infection, delayed wound healing, and extended hospital stays.

7.2 Secondary endpoint: Hb trends in prehabilitated subgroups

Prehabilitation, defined as the enhancement of a patient's functional capacity through targeted interventions before surgery, has been increasingly studied as a strategy to mitigate perioperative risks. Previous studies have demonstrated that prehabilitation can reduce the incidence of postoperative complications and help maintain stable hematologic parameters. The individualized prehabilitation program implemented in this study aimed to enhance the functional capacity of patients scheduled for radical cystectomy by focusing on physical exercise, nutritional support, and psychological care. A critical aspect of this analysis was the evaluation of hemoglobin levels as a marker of overall health and readiness for surgery.

As a secondary endpoint of this pilot study, a focus is proposed between two subpopulations of the sample: group 1, those who at 4 weeks post-surgery present Hb levels < 13vg/dL, and group 2, those who present higher levels. The cutoff has been set at 13 g/dL to define these "newly anemic" patients, regardless of sex, since, as women with a pre-operative Hb of 12 g/dL are twice as likely to require a transfusion compared to men with an Hb of 13 g/dL, this hemoglobin level should be considered suboptimal in surgical settings. It is now emerging, then, that when treating anemia pre-operatively, the target hemoglobin concentration should be ≥13vg/dL in both sexes, to minimize the risk of transfusion- associated unfavorable outcomes[100].
Is it possible that prehabilitation contributes to maintaining elevated hemoglobin levels in oncological patients who are not excessively debilitated?

Hemoglobin levels at baseline play a pivotal role in determining perioperative outcomes. Patients with lower baseline Hb are more likely to develop postoperative anemia. Therefore, stratifying patients based on baseline Hb (G1: <13 g/dL, G2: >13 g/dL) is critical for understanding the differential impact of prehabilitation.
The data from our study demonstrate that while both G1 and G2 benefited from prehabilitation, G2 patients consistently maintained higher Hb levels throughout the perioperative period. This suggests that patients with better baseline hematologic reserves are more likely to withstand the physiological stress of surgery. Specifically, G2 patients had a mean Hb of 13.71 g/dL at discharge compared to 11.22 g/dL in G1 ($p = 0.044$). The fact that G1 patients experienced a more significant drop in Hb levels postoperatively suggests that additional interventions, such as iron supplementation or erythropoietin therapy, may be required for patients with low preoperative Hb.

7.3 Tertiary Endpoint: Postoperative complications and Hb levels

Given these results, we then considered whether baseline Hb levels might impact surgical outcomes, particularly complications within 90 days of the procedure. Our third endpoint sought to explore the relationship between Hb levels and postoperative complications.
The data indicate that patients with higher baseline Hb levels (G2) experienced significantly fewer complications than those in G1. Specifically, only 16.67% of G2 patients had complications compared to 83.33% in G1. Although the difference in specific types of complications (such as delirium, pneumonia and AKI) was not statistically significant, the overall trend is clear: maintaining adequate Hb levels may reduce the likelihood of postoperative complications.
Patients in G1, with lower baseline Hb levels, may have been more vulnerable to complications, despite receiving prehabilitation. The data suggest that while prehabilitation has positive effects on Hb preservation, additional perioperative strategies might be necessary to fully mitigate the risks associated with low Hb .
The data obtained are not sufficient to demonstrate a benefit regarding the incidence of complications among patients with Hb levels >13 g/dL.

7.4 Limitations and future directions

This study has several limitations that should be acknowledged.
Firstly, as a pilot study, its findings are preliminary and require further validation in larger, more comprehensive trials. The limited scope of this research affects the generalizability of the results, particularly because it was not a multicenter study. Conducting the study in a single center may introduce biases related to the specific protocols, patient population, and surgical practices at the institution, which may not be applicable to other settings or regions. Multicenter studies are essential for ensuring that the results can be broadly applied to a wider population.
A significant limitation is the small sample size of only 23 patients. While the study provides valuable insights, the small cohort limits the statistical power to detect meaningful differences or trends, particularly when examining subgroups within the population. The small number of participants also increases the risk that the results could be skewed by

individual patient variations rather than representing broader trends. In a larger cohort, the variability between individuals might be smoothed out, providing more reliable conclusions.
Another key limitation is the lack of overlapping timepoints between the study cohort and the control population. This makes direct comparisons between the groups challenging, as it is difficult to assess whether differences in outcomes are due to the intervention itself or to variations in the timing of data collection. The absence of matched timepoints reduces the reliability of the comparison, as changes in hemoglobin levels and postoperative outcomes may follow different trajectories based on when the data were collected.
Addressing these confounders in future research would provide a clearer understanding of the true impact of the prehabilitation program.

8 Conclusion

This pilot study aimed to evaluate the role of multimodal prehabilitation in optimizing hemoglobin (Hb) levels and reducing postoperative complications in patients undergoing major oncological surgery, specifically cystectomy. The results provide valuable insights into the potential benefits of prehabilitation, though several limitations temper the conclusions. Nonetheless, the study contributes to the growing body of evidence that supports prehabilitation as a key intervention in preparing patients for surgery.

The findings demonstrated that patients who underwent prehabilitation were more likely to maintain higher Hb levels at critical timepoints, such as the day of surgery and discharge. This was particularly evident in the significant differences in Hb levels between the prehabilitation group and the control group, with the former consistently showing better hematologic profiles. Elevated Hb levels are crucial in reducing perioperative anemia, which is linked to delayed recovery, increased infection rates, and overall longer hospital stays. While the observed benefits were notable, the relatively small sample size limits the statistical power of the study.

Despite these limitations, prehabilitation appears to be a promising strategy for improving patient outcomes in oncological surgery. The potential benefits of prehabilitation extend beyond the preservation of Hb levels. By integrating physical exercise, nutritional support, and psychological care, prehabilitation addresses multiple aspects of patient health, thereby enhancing overall functional capacity and resilience. As such, it offers a comprehensive approach to surgical preparation that goes beyond traditional preoperative care. In the context of an aging population, where the burden of chronic diseases and frailty is expected to rise, the importance of optimizing preoperative health cannot be overstated.

The aging population presents a particular challenge for surgical care, as older patients are often more vulnerable to perioperative complications. Age-related declines in functional capacity, combined with comorbid conditions such as anemia or cardiovascular disease, increase the risk of poor surgical outcomes. Prehabilitation offers a proactive solution by strengthening the patient's physical and mental resilience before surgery, thereby reducing the likelihood of complications and promoting faster recovery. Given the increasing prevalence of elderly patients undergoing major surgeries, prehabilitation is likely to become an essential component of preoperative care in the future.

Looking ahead, there is a strong case for prehabilitation to become the gold standard in preparatory management, particularly for high-risk patients such as the elderly or those with significant comorbidities. The ability to personalize prehabilitation programs to address individual patient needs makes it a versatile and effective tool for improving surgical outcomes across a wide range of patient populations. As the healthcare system adapts to the challenges posed by an aging society, it is essential to prioritize interventions like prehabilitation that enhance patient resilience and reduce the strain on healthcare resources. The results of this study, although preliminary, suggest that prehabilitation holds significant potential for improving perioperative care, and future research should focus on larger, multicenter trials to fully establish its efficacy and long-term benefits.

In conclusion, while the current study provides some insights into the role of prehabilitation in surgical care, further research is needed to confirm its impact on postoperative outcomes. However, as the population continues to age and the demand for high-quality surgical care grows, prehabilitation is poised to play a central role in the future: better in, better out.

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