REVIEW PAPER

Nutritional prehabilitation in patient undergoing radical cystectomy: a systematic review for practical urologist

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Introduction Immunonutrition plays a major role in the prehabilitation of patients undergoing radical cystectomy for bladder cancer. The aim of this study was to introduce practitioners to current clinical research on the nutritional preconditioning of patients before surgery.

Material and methods A systematic literature review was conducted in PubMed database. Out of 25 records identified, 7 studies were included. Only 1 of these was a randomised trial.

Results Immunonutrition has been shown to reduce postoperative complications, length of stay in hospital and improve postoperative bowel function. Immunonutrition also has a role in modulating the inflammatory response.

Conclusions Nutritional prehabilitation has a potential positive impact on the course after bladder removal surgery. However, randomised controlled trials are needed to obtain reliable data in this area.

Key Words: prehabilitation ‹› immunonutrition ‹› bladder cancer ‹› radical cystectomy

INTRODUCTION

Bladder cancer is the 7th most commonly diagnosed cancer in men, while it drops to the 10th most common cancer in both sexes are taken into account [1]. The standard treatment for patients with urothelial muscle invasive bladder cancer is radical cystectomy [2]. Urological surgery is highly traumatic, especially in patients with bladder cancer undergoing cystectomy. Although its aim is to cure the disease and reduce symptoms, surgery inevitably exposes patients to physiological, psychological, and cognitive stress with the potential for short- and long-term complications.

Protein-energy malnutrition is currently one of the most complicated problems in surgery, affecting the multimorbid medical population in 30.0% of hospitalized patients [3, 4]. This is due to a number of predisposing factors, including long-term immobilization, advanced age (defined as 65 years or older), lack of appetite, and multiple comorbidities that lead to progressive weight loss and sarcopenia [5]. Malnutrition is a major risk factor that is strongly associated with increased mortality, morbidity, functional disability, prolonged hospitalization, and most importantly, increased healthcare costs [6, 7].

According to international societies, nutritional support should be provided during hospital stay. Ideally, nutritional screening should be performed during the process of qualifying for surgery. Early oral feeding is the preferred mode of nutrition in surgery, particularly in patients at high nutritional risk, especially those undergoing major surgical procedures, such as surgery for cancer, and those with serious complications despite the best perioperative care. From a metabolic and nutritional standpoint, the key aspects of perioperative

care include integrating nutrition into overall patient management, avoiding long periods of preoperative fasting, reintroducing oral nutrition as early as possible after surgery, and prompt initiation of nutritional treatment if nutritional risks arise. Metabolic control, such as blood glucose levels and reducing factors, exacerbate stress-related catabolism or impaired gastrointestinal function, as well as the necessary early mobilization to enhance protein synthesis and muscle function.

"Prehabilitation" aims to reduce metabolic risk, which implies a tri-modal approach including nutrition, exercise and a psychological component [6]. Significant reductions in complications have been shown in older high-risk patients with American Society of Anesthesiologists (ASA) grades III, IV and IV [8]. Meta-analyses have shown that prehabilitation can contribute to a reduction in postoperative complications and length of hospital stay (LOS) in patients undergoing major abdominal surgery.

MATERIAL AND METHODS

This systematic literature review followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [9] and the PRISMA checklist. The search for primary studies, written in English and published between 2014 and 2024, focusing on nutritional prehabilitation interventions tailored for patients scheduled for cystectomy surgery, was conducted across indexed databases: PubMed, on December 8, 2024.

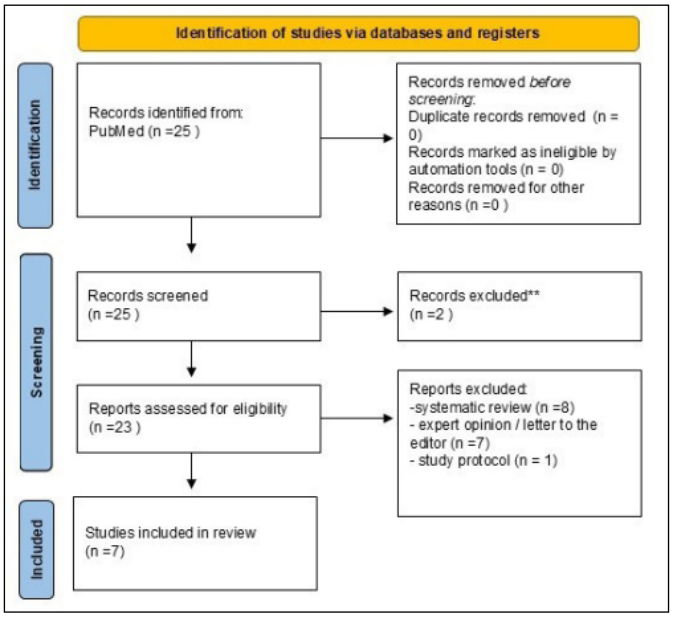

Figure 1. *Flow diagram for systematic review.*

The PubMed database was queried using the following search terms: "immunonutrition" and "radical cystectomy". The exclusion criteria were designed to exclude book chapters, articles for which full-text versions were not available, editorials, and publications with low methodological quality. Therefore, a total of 25 publications were obtained.

After the initial elimination of papers whose titles indicated analyses in areas other than those of interest to the authors, abstracts of 24 publications were reviewed. Of these 24 papers, 1 paper was a description of the protocol for a planned study, 9 of them was review and 6 of them was Expert opinion and letters to the editor. One paper was an early publication of the results that were described and expanded upon in a subsequent publication. Finally, 7 original publications were included in the analysis. The screening process included seven studies and the results are shown in Figure 1.

RESULTS

In a retrospective cohort study Takeuchi et al. [10] retrospectively enrolled 86 patients who underwent radical cystectomy and urinary diversion (ileal conduit) between 2014 and 2021. The patients were divided into an immunonutrition group (n = 43) and a control group (n = 43). Patients in the immunonutrition group received oral supplementation before surgery containing arginine and eicosapentaenoic acid. They compared the levels of arginine and eicosapentaenoic acid in the plasma before and after the operation, and the rate of infection at the surgical site between the 2 groups. The observation period for complications was up to 30 days.

Plasma arginine and eicosapentaenoic acid levels were significantly elevated on the day prior to surgery in the immunonutrition group. However, the plasma arginine levels on the day following surgery were not significantly different between the groups. The incidence of surgical site infection was significantly lower in the immunonutrition group. Multivariate analyses indicated a significant association between site infection and nutritional status. Preoperative immunonutrition was found to significantly reduce the incidence of surgical site infections following radical cystectomy and ileal conduit. After radical cystectomy and other major abdominal surgery, preoperative malnutrition is consistently associated with poor outcomes [10].

In a study involving 78 consecutive patients, Patel et al. [11] analyzed the effects of preoperative immunonutrition and carbohydrate drinks and compared them with 92 historical controls. The preoperative nutrition (PN) group and control groups exhibited

similar distributions of age, sex, American Society of Anesthesiologists physical status classification, clinical stage, and body mass index. Return of bowel function occurred earlier in the PN group than in the control group. It can be concluded that the use of a PN, which includes immunonutrition and a carbohydrate drink, may be associated with an earlier return of bowel function after radical cystectomy. Overall complications, infectious complications, and readmission within 30 days were similar in both the groups. While the length of hospital stay was shorter for those receiving immunonutrition, the difference was not statistically significant.

Khaleel et al. [12] in their work analyzed the role of preoperative immunonutritional supplementation before radical cystectomy. A retrospective review was conducted of 204 patients who underwent radical cystectomy (RC) for bladder cancer. Patients were divided into 2 groups: those who received oral immunonutritional supplementation and those who did not. The outcomes of interest included the development of postoperative complications (Clavien-Dindo III–V), readmission within 30 days, ileus, total parenteral nutrition (TPN) requirement, postoperative infection, and LOS. Patients who received preoperative immunonutritional supplementation had significantly lower total parenteral nutrition requirements and developed fewer postoperative infections. There were no significant differences in other outcomes.

In 2021 Cozzi et al. [13] published their data from a retrospective cohort study of 52 patients who underwent radical cystectomy between April 2016 and December 2017. Because of immunonutrition before radical cystectomy. muscle invasive bladder cancer, 26 patients received perioperative immunonutrition. In conclusion, Cozzi et al. reported that immunonutrition was not associated with lower rates of postoperative complications, length of hospital stay, and total parental nutrition. There was a higher incidence of infections and readmissions to the hospital in patients who received immunonutrition before radical cystectomy.

In a subsequent study, Hamilton-Reeves et al. [14] compared the effect of a brief preoperative specialized immunonutrition with standard oral nutritional supplementation on acute inflammatory response and arginine status in patients undergoing radical cystectomy. In this prospective randomized trial, 14 men received immunonutrition and 15 received only nutritional supplements. The Th1 : Th2 ratio, peak interleukin 6 levels, and plasma arginine levels suggest that specialized immunonutrition counteracts the dysregulated T-helper balance, reduces the inflammatory response, and prevents arginine concentrations induced by radical cystectomy.

In 2017, Lyon et al. [15] published their data on immunonutrition in 40 patients who received arginine shakes 5 days prior to their scheduled cystectomy. They evaluated the safety, tolerability, and adherence to the supplementation regimen. A prospective group of 104 patients who had not received arginine prior to surgery served as the control group. No serious adverse events occurred during the supplementation. Supplementation with immune nutrients was not significantly associated with overall complications, infectious complications, or hospital readmission.

A multicenter, prospective, pilot, case-control study was conducted from December 2012 to June 2013, and the results were described by Bertrand et al. [16]. Thirty patients received immunonutrition for 7 days prior to radical cystectomy in addition to their regular diet. The control group comprised 30 patients who received only a regular diet. The incidence of postoperative complications was significantly lower in the immunonutrition group than in the control group. Complication severity, graded according to the Clavien-Dindo classification, was lower in the immunonutrition group. Infections and paralytic ileus were also significantly less common than in the control group. The length of hospital stay was also significantly shorter in the study group.

A summary of the nutritional prehabilitation interventions and outcomes are shown in Table 1.

DISCUSSION

The LOS is one of the main parameters used to assess the effects of immunonutrition. The LOS was analysed in 5 of the 7 studies reviewed. Patel et al. [11] reported that the median LOS was 6 vs 5 days in the control group. Bertrand et al. [16] showed that the median LOS was 15 vs 17 days in a group without immunonutrition. Although it should be noted that the differences between the groups were not statistically significant. Lyon et al. [15], Cozzi et al. [13], and Khaleel et al. [12] observed no difference in the LOS after radical cystectomy between patients with and without nutritional prehabilitation.

The next parameter that was studied was the presence of postoperative complications. The presence of complications assessed by the Clavien-Dindo classification was analyzed. High-grade complications were defined as those with a Clavien-Dindo grade of III or higher [17].

Aldhaam et al. [18] showed a lower incidence of 30-day high-grade complications (5.0%) in the immunonutrition group than in the control group (16.0%).

In the 3 studies that we analyzed, only 2 found a reduction in postoperative complications in the immunonutrition group. In all 3 cases, the difference was not significant. However, in these studies, it was believed that nutritional prehabilitation reduces the number of postoperative complications. In 1 case, there was only an increase in the number of infections confirmed by microbiological examination in the immunonutrition group [13].

Patel et al. [11], Cozzi et al. [13], and Bertrand et al. [16] reported a faster return of bowel function, which is associated with a reduction in the use of parenteral nutrition. The analysis of hospital readmissions within 30 days was also much better in the group that received nutritional prehabilitation [11, 13].

Hamilton-Reeves et al. [14] showed in their study that immunonutrition plays an important role in reducing the inflammatory response and preventing arginine depletion after radical cystectomy. Nutritional prehabilitation interventions are increasingly recognized as an integral component in optimizing outcomes in patients undergoing radical cystectomy. This complex surgical procedure is associated with significant postoperative morbidity and mortality. Prehabilitation is a tactic designed to improve a patient's overall health and well-being prior to surgery in order to modify likely risk factors, thereby increasing physiological reserve and reducing adverse stress responses [3]. Despite advances in anesthesia, surgical techniques, and perioperative care, most patients do not achieve rapid functional and physiological recovery. Research on risk factors has identified protective elements against surgical complications and postoperative recovery, including good physical fitness, functional reserve, and nutrition [7].

There is evidence that poor physical, nutritional, and psychosocial status negatively affects surgical outcomes. This is exemplified by the case of radical cystectomy for bladder cancer. Single-intervention approaches, such as preoperative exercise or nutrition alone, had no effect on surgical outcomes, such as length of stay or complications. However, multidirectional approaches targeting postoperative functional status have been shown to be effective and safe [19].

Dal Bello et al. [20] conducted a similar analysis of studies of immunonutrition before radical cystectomy. The authors used a different methodology – article search – to analyze 6 studies, 4 of which were also included in our analysis. Their findings regarding immunonutrition before radical cystectomy are consistent with our findings, that current evidence points to a promising role for nutritional prehabilitation interventions in optimizing postoperative outcomes in patients undergoing radical cystectomy.

CONCLUSION

Although there are few multicenter randomized trials of patients undergoing radical cystectomy for bladder cancer in which immunonutrition was used in the preparation, we can conclude from the reviewed papers that such management is effective and

Table 1. *Summary of nutritional prehabilitation interventions and outcome*

No	Author, year	Study country	Study design	NP characteristics	N, number of participants	Outcomes	Results and conclusions
1	Takeuchi et al. 2023 [10]	Japan	Observation retrospective cohort study	ω-3, arginine, nucleotides	n = 86	POC rates, IC	Reduction surgical site infections, no impact on POC
2	Patel et al. 2022 [11]	USA	Observation case-control study	ω-3, arginine, nucleotides	n = 160	POC rates, LOS, IC	Faster return of bowel function, shorter LOS, no impact on POC rates, less IC
3	Khaleel et al. 2021 [12]	USA	Observation case-control study	ω-3, arginine, nucleotides	n = 204	LOS, IC, ReR, TPN	Lower TPN requirement, reduction surgical site infections, no impact on LOS, ReR
4	Cozzi et al. 2021 [13]	Italy	Observation retrospective cohort study	ω-3, arginine, nucleotides	n = 52	POC rates, IC, ReR, LOS	Higher IC and ReR, no impact on LOS, POC, TPN
5	Hamilton-Reeves et al. 2018 [14]	USA	RCT	ω-3, arginine, nucleotides	n = 29	Inflammatory modulation	Lower plasma interleukin 6 concentration, beneficial effect on Th1–Th2 balance, preventing arginine depletion
6	Lyon et al. 2017 [15]	USA	Observation case-control study	ω-3, arginine, nucleotides	n = 144	POC rates, LOS, ReR	No impact on POC, IC, ReR, LOS
7	Bertand et al. 2014 [16]	France	Observation case-control study	ω-3, arginine, nucleotides	n = 60	POC rates, IC, LOS	Reduction surgical site infections, POC, faster return of bowel function, shorter LOS

IC – infections complication; LOS – length of stay; NP – nutritional prehabilitation; POC – postoperative complication; RCT – randomized controlled trial; ReR – readmission rate; TPN – total parenteral nutrition; ω-3 – omega-3 fatty acids

improves the operative course. The use of oral nutritional supplements, immunonutrition, and nutritional counselling has shown some efficacy in improving postoperative outcomes, modulating the inflammatory response, and improving the nutritional status. Nutritional prehabilitation is inexpensive, does not impose an excessive financial burden on the patient, and can be widely used in clinical practice.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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