Sultan *et al. African Journal of Urology* (2024) 30:52
https://doi.org/10.1186/s12301-024-00453-y

African Journal of Urology

ORIGINAL RESEARCH

Outcome of perioperative immune enhancing nutrition in patients undergoing radical cystectomy

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Abstract

Background Since radical cystectomy is associated with relatively high perioperative morbidity and mortality, this study was conducted to evaluate the efficacy of perioperative immune nutrition in radical cystectomy patients on postoperative outcomes including wound healing, postoperative complications, either infectious or non-infectious, and length of hospital stay.

Patients and methods This prospective, randomized controlled study was conducted between June 2022 and November 2023. Forty-two patients who had undergone radical cystectomy with ileal conduit were randomized into two groups: the immune nutrition group, which received perioperative immune nutrition, and the conventional group, which did not receive immune nutrition. Patients were followed up for 30 days postoperatively to assess wound healing, infectious and non-infectious complications, and the length of hospital stay.

Results Patients who received immune nutrition had significantly lower postoperative infectious complications (19.0 vs 61.9%; $P=0.004$), shorter hospital stay (16.57 ± 3.74 vs 20.38 ± 5.97; $P=0.01$) and shorter ICU stay (2.60 ± 1.07 vs 7.09 ± 7.50; $P=0.029$). The proper wound healing was significantly higher in the immune nutrition group (90.5 vs 52.4%; $P=0.006$). However, there was no significant difference between both groups in the rate of non-infectious complications (28.5% vs. 57.1%, $P=0.061$).

Conclusion Perioperative immune nutrition is associated with improved wound healing, reduced infectious complications, and reduced length of hospital stay.

Trial registration clinicaltrials.gov, NCT05822518. Registered 1 April 2023—Retrospectively registered, https://clinicaltrials.gov/study/NCT05822518.

Keywords Bladder cancer, Radical cystectomy, Immune nutrition, Complications, Wound healing

1 Background

Urinary bladder cancer (BC) is the 10th most common malignant tumors. The incidence of BC varies regionally; Egypt, Western Europe, and North America have the highest incidence rates, while Asian countries have the lowest rates [1, 2].

Twenty-five percent of newly diagnosed BC cases are muscle-invasive BC while the remaining 75% are non-muscle-invasive. Radical cystectomy (RC), along with pelvic lymph node dissection, is the cornerstone of the management of muscle-invasive BC. RC plays

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an essential role even in very high-risk and treatment-refractory non-muscle-invasive BC [3, 4].

Although surgical techniques and perioperative care have improved, RC remains one of the most burdensome procedures due to its relatively high perioperative morbidity and mortality rates. Despite the lower mortality rate of RC (0.8–8.3%), early complications have been found in up to 64% of patients such as paralytic ileus, wound infection, wound dehiscence, anemia requiring blood transfusion, urinary tract infection, deep venous thrombosis, pulmonary embolism, pneumonia, urinary leakage or rectal injury [4, 5].

Malnutrition is common among BC patients. Cancer cachexia along with other significant nutritional issues are expected in such patients who are usually of old age. Up to 40% of patients are malnourished when diagnosed with cancer [5, 6].

Immuno-nutrients, such as glutamine, arginine, omega-3 fatty acids, and nucleotides, have been found to reduce pro-inflammatory cytokines and modulate inflammatory response. Therefore, immune nutrition (IN) and improvement of nutritional status play an important role in the wound healing process, shortening the length of hospital stay (LOS), preventing infections, and reducing postoperative complications [7, 8].

The aim of this study was to evaluate the postoperative outcomes in RC patients receiving perioperative nutrition and evaluate its efficacy in improving wound healing, reducing postoperative complications (either infectious or non-infectious), and shortening LOS.

2 Patients and methods

This prospective randomized controlled trial was conducted between June 2022 and November 2023. The study received ethics approval from our local university ethics committee under the number 10/2022UROL18. We obtained informed consent from all patients prior to participating in the study. The study included 42 patients with pathologically proven urinary BC with radiological staging of T2–3, N0, M0 and good performance status (American Society of Anesthesiologists (ASA) score $\leq$ 3 and The Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO) score $\leq$ 2). The included patients were planned for open RC and ileal conduit. Patients with coagulopathy, distant metastasis, body mass index < 18.5, relevant food allergies or severe renal or hepatic insufficiency were excluded. Patients were randomized into two groups: the IN group and the conventional group.

This study consisted of four phases. The 1st phase included detailed preoperative assessment with complete history taking, physical examination, radiological, comorbidity (Charlson comorbidity index, diabetes mellitus and hypertension) and nutritional status assessment (Patient-Generated Subjective Global Assessment (PG-SGA) and body mass index).

The 2nd phase involved preoperative preparation. All patients were admitted to the hospital 3 days before surgery for bowel preparation. Throughout this phase, the IN group was given Neo-mune (containing glutamine, arginine and fish oil, otsuka pharmaceutical) powder 60 g o.d. orally while the conventional group did not receive any IN supplementations.

The 3rd phase involved postoperative management. In this phase, patients in both groups were instructed to nothing per mouth until postoperative flatus or intestinal sounds were audible. Thereafter, they were allowed to start clear fluids then a liquid diet and a regular diet when tolerated. Throughout this phase, the IN group was given Neo-mune powder 60 g o.d. orally for 2 weeks starting when the intestinal sounds were audible and Dipeptiven (containing L-alanyl-L-glutamine dipeptide, Fresenius Kabi pharmaceutical) solution 50 mg o.d. IV for the 5 days following the operation while the conventional group did not receive any IN supplementations.

The patients were followed up postoperatively for 30 days in the 4th phase. Outcomes were assessed as follows: wound healing according to the Pressure Ulcer Scale for Healing (PUSH) tool, postoperative complications (infectious and non-infectious complications such as paralytic ileus, anemia, transient elevation of serum creatinine, etc.) assessed and graded by modified Clavien–Dindo classification, LOS and ICU stay.

All data were collected, tabulated, and statistically analyzed using IBM SPSS software package version 20.0. Qualitative data were described as numbers and percentages. The Chi-square test, Fisher's exact or Monte Carlo correction were used for categorical variables. Student's *t*-test and Mann–Whitney test were used for quantitative variables. The results with a *P*-value less than 0.05 were considered statistically significant.

3 Results

This study included 56 patients who underwent RC. Nine of them were excluded as demonstrated in the CONSORT flowchart (Fig. 1). The remaining 47 patients were randomized into 2 groups, the IN group who received perioperative IN and the conventional group who did not receive IN. Five patients were non-compliant to follow-up or discontinued intervention.

There was no statistically significant difference between both groups regarding age, sex, smoking status, ASA score distribution, ECOG/WHO score distribution, Charlson comorbidity index, preoperative nourishment status, body mass index, preoperative

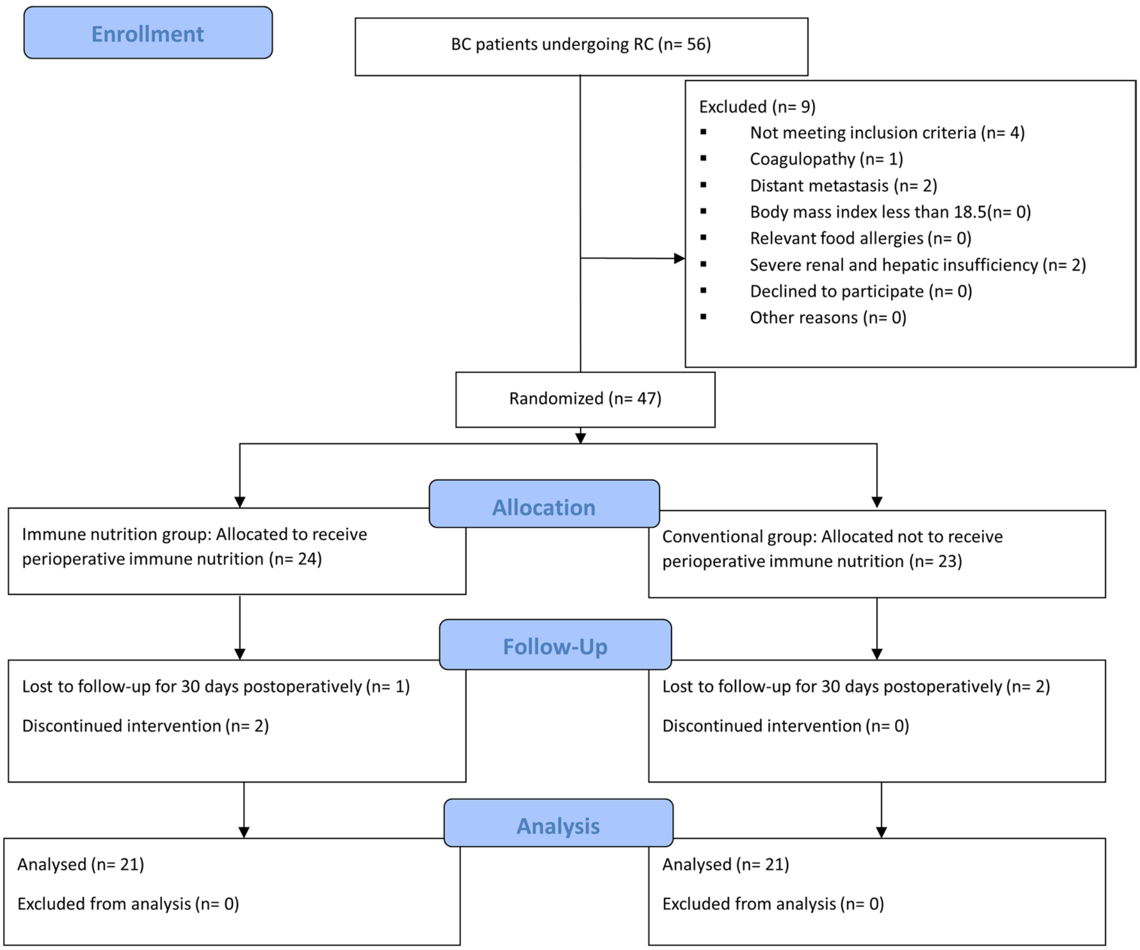

Fig. 1 CONSORT flowchart

radiological data, including tumor size on CT, and presence of hydronephrosis (Table 1).

Proper wound healing was significantly higher in the IN group compared to the conventional group (90.5 vs. 52.4%; $P=0.006$). Infectious complications were significantly lower in the IN group: 19.0% versus 61.9% in the conventional group ($P=0.004$). LOS was shorter in the IN group compared to conventional group (16.57 ± 3.74 vs 20.38 ± 5.97; $P=0.01$). Additionally, ICU stay was shorter in IN group compared to conventional group (2.60 ± 1.07 vs 7.09 ± 7.50; $P=0.029$) (Table 2).

There was no statistically significant difference in the postoperative non-infectious complication rates between the IN and conventional groups (Table 2).

The severity of the complications was graded according to the modified Clavien–Dindo classification and there was no significant difference between both groups apart from wound infection ($P=0.01$) (Table 3).

4 Discussion

RC is one of the most challenging surgical procedures. The surgical principles of RC and minimally invasive techniques have been refined. However, morbidity remains high after RC [4].

Cachexia and progressive deterioration in nutritional status are common among surgical cancer patients and are often known to be the most important indicators of malnutrition. Malnutrition is present at the time of diagnosis of cancer in approximately 15–40% of cases, and this incidence increases up to 40–80% during treatment [6].

Immune-enhancing nutrition can modulate inflammatory and immune responses in cancer patients by decreasing acute toxicity and improving surgical outcomes [7, 9].

In this study, we evaluated the impact of perioperative IN in patients undergoing RC and its efficacy in reducing

Table 1 Population characteristics

	Conventional group ($n=21$)	IN group ($n=21$)	*P* value
Age [mean ± SD] years	64.0 ± 4.68	63.62 ± 5.69	0.814
Sex			0.292
Male	14 (66.7%)	17 (81.0%)	
Female	7 (33.3%)	4 (19.0%)	
Smoking			0.190
Smoker	12 (57.1%)	16 (76.2%)	
Non-smoker	9 (42.9%)	5 (23.8%)	
Charlson comorbidity index			0.770
Score = 3	3 (14.7%)	3 (14.7%)	
Score = 4	9 (42.7%)	8 (38%)	
Score = 5	8 (38%)	7 (32.6%)	
Score = 6	1 (4.6%)	3 (14.7%)	
Diabetes mellitus	2 (9.5%)	3 (14.3%)	1.000
Hypertension	1 (4.8%)	3 (14.3%)	0.606
Performance status (ASA Score)			0.220
ASA 1	14 (66.7%)	15 (71.4%)	
ASA 2	4 (19.0%)	6 (28.6%)	
ASA 3	3 (14.3%)	0 (0%)	
Performance status (ECOG/WHO score)			0.831
Score 0	1 (4.7%)	2 (9.4%)	
Score 1	14 (66.7%)	13 (62%)	
Score 2	6 (28.6%)	6 (28.6%)	
Nutritional status			0.061
Well nourished (PG-SGA Score < 9)	12 (57.2%)	6 (28.6%)	
Malnourished (PG-SGA Score ≥ 9)	9 (42.8%)	15 (71.4%)	
Body mass index (kg/m^2)			0.549
Normal (18.5–24.9)	6 (28.6%)	9 (42.8%)	
Overweight (25–29.9)	9 (42.8%)	6 (28.6%)	
Obese (≥ 30)	6 (28.6%)	6 (28.6%)	
Tumor size (by CT)			0.532
Small mass (mass diameter < 3 cm)	8 (38.0%)	10 (47.6%)	
Large mass (mass diameter < 3 cm)	13 (62.0%)	11 (52.4%)	
Hydronephrosis	10 (47.6%)	10 (47.6%)	1.000

ASA American Society of Anesthesiologists, *ECOG/WHO* The Eastern Cooperative Oncology Group/World Health Organization, *PG-SGA*, Patient-Generated Subjective Global Assessment, *CT* computed tomography

postoperative infectious and non-infectious complications, impaired wound healing, and LOS.

Despite perioperative antimicrobial prophylaxis, postoperative infectious complications remain at considerable rates. The risk of infectious complications following RC is estimated to be up to 25–44% [10].

In our study, patients in the IN group had fewer infectious complications than in the conventional group ($P=0.004$). Additionally, wound infections were significantly lower in IN group ($P=0.014$).

In agreement with our study, Bertrand et al. found that infections were lower in the IN group compared to the non-IN group ($P=0.008$) [5]. In the study done by Hamilton-Reeves et al., there was a 39% reduction in infection rate ($P=0.027$) [11]. Similarly, Takeuchi et al. and Khaleel et al. found that preoperative IN significantly reduced the incidence of wound infections [12, 13].

On the contrary, Lyon et al. and Petal et al. found that immune-nutrient supplementation was associated with non-significantly lower postoperative infectious complications [14, 15].

Although the above-mentioned studies found that IN decreased postoperative infection either significantly or insignificantly, Cozzi et al. showed that infections were significantly higher in IN patients ($P=0.009$). These results may be because 92.31% of IN group patients

Table 2 Postoperative outcomes

	Conventional group (*n* = 21)	IN group (*n* = 21)	*P* value
Wound healing			0.006*
Proper healing (PUSH score = 0)	11 (52.4%)	19 (90.5%)	
Impaired healing (PUSH score > 0)	10 (47.6%)	2 (9.5%)	
Infectious complications			
Wound infection	9 (42.9%)	2 (9.5%)	0.014*
Pneumonia	1 (4.8%)	0 (0%)	1.000
Urinary tract infection	5 (23.8%)	2 (9.5%)	0.410
SIRS (without confirmed infection source)	1 (4.8%)	0 (0%)	1.000
Patients experienced infectious complication(s)	13 (61.9%)	4 (19.0%)	0.004*
Non-infectious complications	12 (57.1%)	6 (28.5%)	0.061
LOS (days)			0.018*
Mean ± SD	20.38 ± 5.97	16.57 ± 3.74	
Median	18.0	15.0	
ICU admission	11 (52.4%)	10 (47.6%)	0.757
Length of ICU stay (days)			0.029*
Mean ± SD	7.09 ± 7.50	2.60 ± 1.07	
Median	5.0	2.0	

PUSH pressure ulcer scale for healing, *SIRS* systemic inflammatory response syndrome, *LOS* length of hospital stay, *ICU* intensive care unit

* Statistically significant at $p \leq 0.05$

Table 3 Postoperative complications according to modified Clavien–Dindo classification

Complications	Grade	Conventional group (*n* = 21)	IN group (*n* = 21)	*P* value
Paralytic ileus	I	1 (4.8%)	1 (4.8%)	1.000
Superficial wound infection	I	9 (42.9%)	2 (9.5%)	0.014*
Transient elevation of serum creatinine	I	2 (9.5%)	1 (4.8%)	1.000
Anemia (required blood transfusion)	II	3 (14.3%)	2 (9.5%)	1.000
UTI	II	5 (23.8%)	2 (9.5%)	0.410
DVT	II	1 (4.8%)	0 (0%)	1.000
Pneumonia	II	1 (4.8%)	0 (0%)	1.000
Re-exploration for urinary leakage	III	1 (4.8%)	0 (0%)	1.000
Burst abdomen	III	4 (19.0%)	1 (4.8%)	0.343

UTI urinary tract infection, *DVT* deep venous thrombosis

* Statistically significant at $p \leq 0.05$

preoperatively versus only 3.85% postoperatively were completely adherent to IN consumption [16].

Despite advances in surgical techniques and perioperative care, RC has been followed by relatively high morbidity and mortality rates. postoperative complications are either early complications, which occur within 30 days postoperatively, or late complications, which occur between 30–90 days. It has been reported that 30–70% of complications occur following RC [17, 18].

Regarding early postoperative non-infectious complications, although our study showed that the IN group had non-significantly lower non-infectious complication rates compared to the control group ($P = 0.061$), the ratio between both groups of 2:1 (12 vs. 6 patients) appears to be clinically significant.

Similar results were found by Ritch et al. and Takeuchi et al. who showed that preoperative IN did not reduce postoperative complications significantly [13, 19]. Additionally, Cozzi et al. found that 73.08% experienced one or more complications in both groups (P = 1) [16].

Contrary to our results, Bertrand et al. reported that the postoperative complication rate was significantly lower among the IN patients ($P = 0.008$) [5].

In our study, the LOS was shorter in the IN group compared to the conventional group ($P=0.01$), which was similar to the results found by Bertrand et al., who found that the median LOS was significantly shorter in one of their sample group ($P=0.02$) [5].

Conversely, the LOS in the study by Petal et al. was shorter in the IN group but not statistically significant which was likewise found by Ritch et al. ($P=0.88$) [14, 19].

Although the clinical relevance of IN may lie in enhancing wound healing, to the best of our knowledge, no previous study has evaluated the effect of perioperative IN on either wound healing, or the length of postoperative ICU stay in patients undergoing RC. However, Farreras et al., who tested the effect of IN on wound healing enhancement in gastric cancer surgery, found that surgical wound healing complications significantly decreased among IN patients ($p=0.005$). This was similar to our study which found that IN supplements significantly decreased wound healing complications, such as evisceration, wound dehiscence, or suture failure ($P=0.006$) [20].

Postoperative ICU admission was not routine. However, half of the patients required ICU admission either for close postoperative monitoring or management of sepsis. Although there was no significant difference between both groups regarding the number of ICU admissions, IN group needed shorter ICU stay compared to the control group ($P=0.029$). This was similarly proven by Giger et al. who evaluated the effect of IN in patients with major abdominal surgery. Giger et al. found that there was a significant reduction in the length of ICU stay in favor of the IN group ($p<0.05$) [21].

We believe that this difference between the two studied groups in both LOS and ICU stay was due to the significant reduction in infections as well as improved wound healing.

Although our study is a prospective randomized study and the IN products were available and inexpensive with limited reported adverse effects, there were some limitations including the difference of the surgical situations, such as different operative times or anesthesia complications, and the relatively small sample size. The limited number of cases may be due to the presence of another treatment option for muscle-invasive BC, tri-modality treatment, which was preferred by some patients.

Although there are few studies evaluating the effect of IN in patients undergoing RC, IN proved very promising effects on different outcomes. Consequently, we recommend further studies to be done on larger sample sizes.

5 Conclusion

Perioperative IN was associated with improved wound healing, decreased postoperative infectious complications, and reduction of postoperative LOS, and ICU stay with no significant reduction in postoperative non-infectious complications.

Abbreviations

BC	Bladder cancer
RC	Radical cystectomy
IN	Immune nutrition
LOS	Length of hospital stay
ASA	American Society of Anesthesiologists
ECOG/WHO	The Eastern Cooperative Oncology Group/World Health Organization
PG-SGA	Patient-Generated Subjective Global Assessment
PUSH	Pressure Ulcer Scale for Healing
ICU	Intensive care unit

Acknowledgements

The authors would like to express gratitude towards all the patients who took part in this study.

Author contributions

SS conceived and designed the analysis and contributed data. BS contributed data and contributed in writing of the manuscript. EA conceived and designed the analysis. AA collected the data and contributed in writing of the manuscript. MS contributed data and performed the analysis.

Funding

No funding was received for conducting this study or to assist with the preparation of this manuscript.

Availability of data and materials

All data used in this study are available when asked from the corresponding author after approval from our institute.

Declarations

Ethics approval and consent to participate

The study received ethics approval from the Menoufia University Faculty of Medicine Ethics Committee under the number 10/2022UROL18. We obtained informed consent from all patients prior to participating in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 24 May 2024 Accepted: 3 September 2024
Published online: 18 September 2024

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