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Impact of Perioperative Immunonutrition on Complications in Patients Undergoing Radical Cystectomy: A Retrospective Analysis.

Gabriele Cozzi, MD[1], Gennaro Musi, MD[1,2], Martina Milani[1], Costantino Jemos[1], Sara Gandini, PhD[1,2], Ludovica Mazzoleni[3], Matteo Ferro, PhD[1], Stefano Luzzago, MD[1,2], Roberto Bianchi, MD[1], Emanuela Omodeo Salé[1], and Ottavio de Cobelli, PhD[1,2]

Abstract

Introduction: Radical cystectomy (RC) is the gold standard treatment for patients with muscle-invasive or refractory non-muscle invasive bladder cancer. It is estimated that approximately 64% and 13% of RC patients experience any complication and major complications, respectively. Specialized immunonutrition (SIM) aims to reduce the rates of complications after RC. We reported surgical complication rates in RC patients who received (SIM group) versus who did not receive (no-SIM group) perioperative SIM. Moreover, we investigated factors associated with complications after RC. **Material and Methods:** This is a retrospective cohort study of 52 patients who underwent RC between April 2016 and December 2017. Overall, 26 (50%) patients received perioperative SIM. We recorded age, gender, Charlson Comorbidity Index (CCI), body mass index (BMI), Malnutrition Universal Screening Tool (MUST) score, unintentional weight loss (UWL), SIM drinks consume, surgical approach, urinary diversion, neoadjuvant chemotherapy (NAC), use of total parenteral nutrition (TPN), final pathology, length of stay (LOS), and complications. **Results:** SIM was associated with higher rates of documented infections ($P = .03$). Conversely, post-operative ileus was associated with higher rates of overall infections ($P = .03$). Median LOS was comparable within the 2 groups. Overall, 4 (15.38%) versus 0 (0%) patients in SIM versus no-SIM group were readmitted to hospital ($P = .03$). Age, CCI, NAC, and TPN were not associated with complication rates. **Conclusions:** SIM is not associated with lower rates of post-operative complications in RC candidates. Moreover, higher rates of documented infections were observed in the SIM group. Patients with post-operative ileus experienced more infections. Age, CCI, NAC, and TPN were not predictive of complications.

Keywords

radical cystectomy, bladder cancer, immunonutrition, complications, infections, enhanced recovery after surgery

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Introduction

Radical cystectomy (RC) with pelvic lymphadenectomy is the gold standard treatment for patients with muscle-invasive bladder cancer or non-muscle invasive disease refractory to intravesical therapy.[1,2]

Up to 64% of RC patients experience overall complications. Of those, 13% experience major complications, namely: sepsis, urinary tract infection, pulmonary embolism, paralytic ileus, intestinal anastomosis fistula, wound dehiscence, lymphocele, diversion necrosis, rectal injury, pneumonia or deep vein thrombosis.[3]

[1]European Institute of Oncology, IRCCS, Milan, Italy
[2]Università degli Studi di Milano, Milan, Italy
[3]Università degli Studi di Pavia, Pavia, Italy

Corresponding Author:
Gabriele Cozzi, Division of Urology, European Institute of Oncology, IRCCS, Via Ripamonti 435, Milan, 20141, Italy.
Email: gabriele.cozzi@ieo.it

RC candidates are usually affected by several comorbidities.[4] Moreover, malnutrition was previously associated with higher rates of adverse events after surgery.[5] Malnutrition is a condition in which the intake of calories, proteins or other nutrients is inadequate to meet requirements for tissue maintenance and repair.[6] RC is associated with significant catabolic changes as net fat oxidation and lean tissue lost.[7] Specifically, the use of intestinal segments for urinary diversions impairs gut function and metabolism, leading to higher risks of infection and rapid muscle wasting.[8] Additionally, the immune system of RC patients is hampered by age-related reduction in adaptive immunity, anergic immune activation, and functional decline.[9] Last, neoadjuvant chemotherapy (NAC) may represent another stressful event.[6,10]

In order to optimize peri-operative care, enhanced recovery after surgery (ERAS) pathways have been introduced in urology.[11,12] As part of these protocols, specialized immunonutrition (SIM) drinks, which aim to improve patient's immune function, appear to reduce complications after RC, especially infections.[13] SIM drinks consist of standard nutrition preparations added with specific nutrients, such as arginine, omega-3 fatty acids and glutamine.[14] Although SIM has been shown to upregulate host immune response, modulate inflammatory response, and improve protein synthesis after surgery, its role within an ERAS pathway after RC remains unclear.[14]

Aim of this study is to report the incidence of surgical complications in RC patients who received perioperative SIM compared with patients who did not, and to investigate factors associated with complications.

Materials and Methods

The records of patients who underwent RC at our institution were reviewed. We identified 52 patients who received RC between April 2016 and December 2017. Of those, the first 26 patients (50%) did not received SIM (no-SIM group), while the subsequent 26 (50%) received perioperative SIM (SIM group) with Impact Oral® (Nestlé Health Science).

All patients were managed according to an ERAS protocol including early nasogastric tube removal, monitoring of total amount of intravenous fluids administered, prokinetics drugs, reduced use of opioids, early feeding, and early ambulation.

Patients in the SIM group were supposed to consume Impact Oral® 3 times a day for 7 days preoperatively (in addition to their regular diet) and twice a day for 7 days postoperatively. The expenses for SIM were incurred by our Institution.

For each patient, we recorded age, gender, Charlson Comorbidity Index (CCI), body mass index (BMI), Malnutrition Universal Screening Tool (MUST) score, unintentional weight loss (UWL) (difference between usual weight and weight at preoperative evaluation), number of SIM drinks consumed pre- and postoperatively, surgical approach (open or robot-assisted), type of urinary diversion, use of NAC, use of post-operative total parenteral nutrition (TPN), final pathology of the disease, length of stay (LOS), post-operative complications, and readmission rates. Among complications, infections were defined as the need for intervention or prescription of nonprophylactic antibiotics. Furthermore, we distinguished infections documented by culture tests or imaging versus clinical conditions with fever and leukocytosis but negative investigations.

Descriptive statistics, with frequencies, medians, and interquartile ranges, are presented to describe socio-demographic or clinical features, tumor characteristics and treatments in SIM and no-SIM groups. Categorical variables were reported as absolute and relative frequencies (percentages), whereas continuous variables were summarized with medians and interquartile ranges (IQR: 25th-75th percentiles). Differences between SIM and no-SIM patients were evaluated with Chi-squared tests or Fisher exact tests for categorical variables and Wilcoxon rank test for continuous variables. Univariate analyses and multivariable logistic models were applied to investigate factors associated with higher rates of infections. Two-sided *P*-values are presented.

Results

Population characteristics are reported in Table 1.

Males account for the majority of patients within each group (80.77%). Median age was 68 (IQR: 57-71) versus 68 years (IQR: 63-71) for SIM versus no-SIM patients, respectively. Eleven patients (42.31%) in the SIM group received NAC, while 12 patients (46.15%) received NAC in the no-SIM group. Robot-assisted surgery was performed in 9 (34.61%) versus 7 (26.92%) patients in SIM versus no-SIM groups, respectively.

No patients within the SIM group had a BMI lower than 20 kg/m^2. Conversely, in the no-SIM group, 1 (3.85%) and 3 (11.54%) patients had a BMI $<18.5\,kg/m^2$ and a BMI between 18.5 kg/m^2 and 20 kg/m^2, respectively. Obese patients (BMI $>30\,kg/m^2$) were equally distributed (19.23%) within the 2 groups.

UWL was <5%, 5% to 10%, and >10% in 21 (80.77%), 4 (15.38%), and 1 (3.85%) patients in the SIM-group, respectively. Conversely, in the no-SIM group, UWL was <5%, 5% to 10%, and >10% in 25 (96.15%), 1 (3.85%), and 0 patients, respectively. All patients with a UWL > 5% had a BMI $> 25\,kg/m^2$.

In the SIM group, MUST score was 0, 1, and 2 in 24 (92.31%), 1 (3.85%), and 1 (3.85%) patients, respectively. In the no-SIM group, MUST score was 0 and 2 in 23 (88.46%) and 3 (11.54%) patients, respectively.

Table 1. Characteristics of the Included Population.

	SIM group	No-SIM group	*P* value
Number of patients, n (%)	26 (100)	26 (100)	
Age, median (IQR)	68 (57; 71)	68 (63; 71)	.79
Gender			
Male, n (%)	21 (80.77)	21 (80.77)	1
Female, n (%)	5 (19.23)	5 (19.23)	
Body mass index	25.18 (24.2-28.6)	26.62 (22.4-29.6)	.95
Charlson comorbidity index, median (IQR)	5 (3; 6)	5 (4; 5)	.45
Tumor staging			
T0	2	6	.37
Ta, Tis, T1	6	8	
T2	5	2	
T3	9	8	
T4	4	2	
Neoadjuvant chemotherapy	11 (42.31%)	12 (46.15%)	.78
Urinary diversion			
Ureterocutaneostomy, n (%)	2 (7.69)	2 (7.69)	
Ureteroileocutaneostomy, n (%)	13 (50)	10 (38.46)	
Neobladder, n (%)	11 (42.31)	14 (53.85)	
Robotic approach, n (%)	9 (34.61)	7 (26.92)	.55

Table 2. Complications Occurred in 2 Groups, Reported According to the Clavien-Dindo Classification.

Complication	Clavien-Dindo grade	SIM group n (%)	No-SIM group n (%)	*P* value
Infection	II	12 (46.15)	6 (23.08)	.08
Only clinical symptoms	II	2 (7.69)	4 (15.38)	.04
Documented infection	II	10 (38.46)	2 (7.69)	.009
Hematoma	II	1 (3.85)	1 (3.85)	1
Blood transfusion	II	12 (46.15)	10 (38.46)	.57
Ileus	II	7 (26.92)	3 (11.54)	.16
Deep venous thrombosis	II	3 (11.54)	2 (7.69)	.64
Pulmonary thromboembolism	II	2 (7.69)	1 (3.85)	.55
Urinary fistula	IIIa	4 (15.38)	5 (19.23)	.71
Urinoma	IIIa	2 (7.69)	2 (7.69)	1
Lymphocele (symptomatic)	IIIa	2 (7.69)	1 (3.85)	.55
Bowel fistula	IIIb	3 (11.54)	1 (3.85)	.29
Wound dehiscence	IIIb	0 (0)	1 (3.85)	.31

Median CCI was 5 (range: 3-9) versus 5 (range: 1-6) in SIM versus no-SIM groups, respectively.

Twenty-four patients (92.31%) consumed all the preoperative SIM drinks, while 2 patients (7.69%) showed an adherence between 80% and 100%. Among patients with 100% adherence, 4 (15.38%) suffered from diarrhea[13] and 8 (30.77%) from nausea.

Postoperatively, only 1 patient (3.85%) had a 100% adherence to SIM assumption, while 2 (7.69%), and 23 (88.46%) patients had an adherence between 80% and 100% and below 80%, respectively.

Nineteen patients (73.08%) experienced 1 or more complications in both groups ($P=1$). Complications are reported in Table 2 according to the Clavien-Dindo classification.[15]

Median LOS was 10 (IQR: 9-16) days in the SIM group and 10 (IQR: 9-13) days in the no-SIM group ($P=.39$). Four (15.38%) and 0 (0%) patients were readmitted to hospital in the SIM versus no-SIM group ($P=.03$).

Age, CCI, and NAC were not associated with higher complication rates. Overall infections occurred in 46.15% versus 23.08% patients in the SIM versus no-SIM group, respectively ($P=.08$). Documented infections occurred in 38.46% versus 7.69% in the SIM versus no-SIM group, respectively ($P=.009$; Figure 1).

The use of TPN was not different between groups (23% vs 15% in SIM vs no-SIM groups, $P=.48$). However, patients who received TPN (n=10) had higher rates of overall (70% vs 26% for TPN vs no TPN; $P=.009$) and

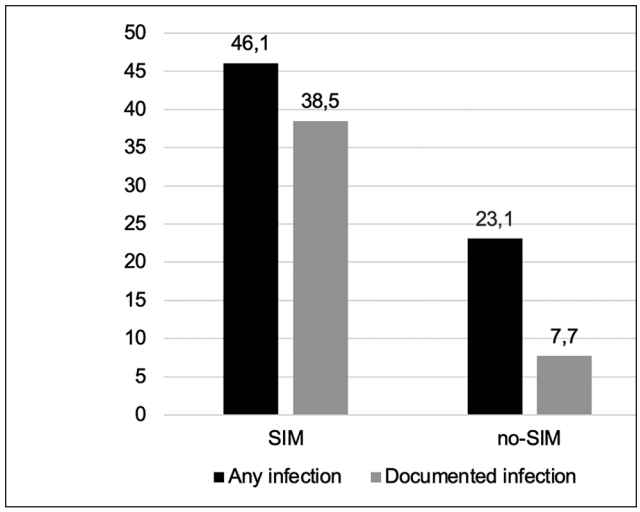

Figure 1. Bar plot of percentages of infection by SIM group.

documented infections (50% vs 16.7% for TPN vs no TPN; $P = .02$). Specifically, of the 5 documented infections in the TPN group, 1 was found in a wound swab, 1 from urine culture, 1 from drain fluid and only 2 from blood culture and, in consequence, TPN-related. These 2 patients were equally distributed between the SIM and the no-SIM groups.

In multivariable logistic regression models, patients who experienced post-operative ileus presented higher rates of infections ($P = .03$—Table 3). Moreover, the SIM group was associated with higher rate of documented infections ($P = .03$—Table 3).

Discussion

In our cohort, 73.08% of patients experienced overall complications, a rate slightly higher than those previously reported. Infections occurred in 46.15% versus 23.08% of patients in the SIM versus no-SIM group, respectively ($P = .08$). To provide a more detailed analysis, we distinguished between infections diagnosed only by clinical symptoms and infections documented by cultural exams (eg, urine culture, blood culture, swab, etc.). Indeed, documented infections occurred in 38.46% versus 7.69% in the SIM versus no-SIM group, respectively ($P = .009$).

Readmission rate was also significantly higher in the SIM group (15.38% vs 0%—$P = .03$). No significant differences between the 2 groups were observed regarding other types of complication.

It is known that RC is burdened by significant morbidity. Specifically, infections represent the most common adverse event after this kind of surgery,[16] accounting for 25% of complications within 90 days after RC.[13]

A role in the genesis of these complications may be played by the imbalance of the immune system. Surgery causes the release of stress hormones and inflammatory mediators, such as cytokines. The systemic inflammatory response syndrome, which is the cytokine response to infection and injury, has a major impact on metabolism.[17] Major surgery disrupts the Th1 to Th2 balance to a predominantly Th2 response due to elevated IL6 levels, impairing cell-mediated immunity and increasing the susceptibility of the patient to infections.[18,19] The expansion of myeloid-derived suppressor cells also causes similar events.[13]

Much effort has been put in trying to reduce complications. ERAS protocols have been suggested to reduce LOS, time to bowel function and complication rates after RC.[20] Although sufficient evidence exists within colorectal surgery to support ERAS, the only randomized controlled trial (RCT) including RC patients closed prematurely due to poor accrual without showing significant differences in terms of complication rate, LOS, or return to bowel function.[21] Some ERAS protocols include SIM, which is a nutritional support that aims to improve patient's immune system.[5] Nutrition therapy may be indicated even in patients without obvious disease-related malnutrition. Specifically, patients who cannot maintain appropriate oral intake for a long period perioperatively could be considered ideal candidates for nutritional support. Furthermore, patients undergoing surgery may be affected by chronic low-grade inflammation as in cancer, diabetes, renal, and hepatic failure.[22] Perioperative supplementation with SIM containing L-arginine, omega-3 fatty acids, vitamin A, and dietary nucleotides derived from yeast RNA may restore the Th1 to Th2 balance and reduce IL6 concentrations.[13,19] An increase in ornithine, which is a product of arginine metabolism by arginase, also provides greater availability of proline and polyamines, contributing to collagen formation and thus to wound healing.[23]

SIM in surgical practice has been mostly established in the perioperative management of major gastrointestinal, head and neck, and cardiac surgery,[1,24-28] while its role in RC patients is still debated.

Bertrand et al compared RC patients who received 3 doses of arginine-containing formula per day in the 7 days prior to surgery with patients who did not receive any supplement. Patients who received SIM had overall post-operative complication rates of 40%, compared to 76.7% for patients who did not receive supplement ($P = .008$). Specifically, a significant reduction was observed for paralytic ileus and postoperative infections.[26]

Hamilton-Reeves et al conducted a prospective RCT in 2016. Patients undergoing RC who received a nutritional supplement containing arginine were compared to patients who received a nutritional supplement without arginine. While no differences in terms of overall complication rates were detected within 30 days after surgery, a 39% reduction in the late postoperative infection rate was observed in patients who received the arginine-containing nutritional

Table 3. Results of Multivariable Logistic Models to Assess Factors Associated with Infections.

		OR	Low 95% CI	Up 95% CI	*P*-value
Any infection					
SIM groups	SIM vs no-SIM	2.37	0.67	8.39	.18
Ileus	Yes vs No	5.71	1.21	27.03	.03
Documented infection					
SIM groups	SIM vs no-SIM	6.54	1.21	35.17	.03
Ileus	Yes vs No	4.00	0.81	19.61	.09

Abbreviations: OR, odd ratio; CI, confidence intervals; SIM, specialized immunonutrition.

supplement. In this group, the balance of Th1 to Th2 cells was maintained at the time of RC. A similar phenomenon was not observed in the control group. Moreover, the plasma concentration of IL6 was significantly lower in patients receiving SIM. Last, patients who received the arginine-containing nutritional supplement fewer myeloid-derived suppressor cells.[13]

Several other reports did not show any advantage with the use of SIM for RC candidates.

Lyon et al reported data of 40 patients who consumed 4 high-arginine immunonutrient shakes per day for 5 days prior to RC, compared with a cohort of 104 prospectively identified non-supplemented RC patients. Preoperative supplementation was safe and well tolerated, but not associated with lower postoperative infectious complications.[29]

In a study by Maffezzini et al,[30] the postoperative enteral administration of Impact® through a jejunostomy showed no effect on the recovery of bowel function, postoperative albumin depletion, or lymphocyte counts, and did not reduce the complication rates.

RC patients are often affected by several comorbidities, which are proportionally associated with worse pathologic and clinical outcomes.[4] Age and comorbidities were reported as predictors of LOS, likelihood of readmission and non-home-based discharge.[31] In our cohort, age and CCI were not independent predictors of complications.

Gastrointestinal dysfunction is commonly seen after RC and remains the most prevalent cause of delayed enteral feeding and discharge.[32] Postoperative total parenteral nutrition might appear an ideal strategy to control and reverse malnutrition. However, no previous analyses showed any advantage with the use of TPN to reverse or control weight loss in cancer patients.[33]

Moreover, TPN has been previously associated with higher rates of post-operative infections after RC, due to impairment of the immune system, and hyperglycemia.[32,34,35] Our findings did not support the aforementioned observations. On the other hand, post-operative ileus, which is the most common gastrointestinal complication after RC, has been found to be associated with a higher incidence of documented infection. Therefore, our results suggest that ileus, sometimes associated with other complications, can be the cause of infections rather than TPN itself.

Many concerns have been raised about a possible increased risk of perioperative morbidity and mortality associated with NAC use.[36-38] Specifically, at least one-third of patients treated with cisplatin-based NAC experience severe hematologic or gastrointestinal effects.[39]

However, there is conflicting evidence about a direct link between NAC and post-operative complications.

Smith et al,[38] examined a cohort of 227 patients who underwent robot-assisted RC and identified NAC as a predictor of overall and major complications. Furthermore, according to an analysis of 939 patients from the Robotic Cystectomy Consortium database, NAC was an independent predictor of any grade and high-grade complications.[37]

Opposite findings were observed in a RCT by Grossman et al[39] comparing patients receiving RC alone versus patients receiving NAC + RC. Authors showed no significant differences in terms of rates and severity of postoperative complications between the 2 groups.

In 2013, Johnson et al performed a retrospective review of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database to identify patients receiving NAC before RC from 2005 to 2011. NAC was not a predictor of complications, re-operation, wound infection, wound dehiscence or increased operating time. Furthermore, patients undergoing NAC had a decreased LOS.[40]

In 2014, Tyson et al reported data of 122 patients from the National Surgical Quality Improvement Program database who had NAC + RC. NAC was not associated with perioperative complications. However, increasing rates of cisplatin-related neurotoxicity[41] leading to peripheral nerve deficits were observed.

In the same year, Gandaglia et al conducted a study relying on the Surveillance and End Results (SEER)-Medicare insurance program linked database and focusing on patients treated with RC within 12 months from diagnosis between January 2000 and December 2009. Three-thousand-sixty patients were included, and 30-days and 90-days perioperative outcomes were evaluated. Neoadjuvant chemotherapy was not associated with significant differences in terms of

complications, blood transfusions, LOS, readmission or mortality.[36]

Similarly, we did not see higher complication rates in patients treated with NAC.

Some limitations need to be acknowledged. The nature of our study is retrospective and, in consequence, influenced by inherent selection bias. The sample size is quite small, even if is similar to other cohorts reported in the available literature. The overall incidence of complications in both groups is slightly higher than reported in the literature.[3] The compliance to postoperative SIM was very low. In consequence, alternative ways of postoperative administration of SIM should be investigated in furthers studies, as Maffezzini et al[30] did using a jejunostomy. The balance of Th1 to Th2 cells and the concentration of serum IL6 was not tested in our cohort, differently from the landmark RCT by Hamilton-Reeves et al.[19]

In conclusion, in our cohort, SIM did not improve postoperative outcomes after RC. Conversely, documented infections were higher in the SIM group. Patients who experienced post-operative ileus exhibited higher rates of overall infections. Age, CCI, NAC, and TPN were not predictors of complications.

Declaration of Conflicting Interests

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Ethics Statements

The study underwent a retrospective review by the European Institute of Oncology Institutional Review Board and was approved (UID 2776).

ORCID iD

Gabriele Cozzi https://orcid.org/0000-0001-6386-7013

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