Preoperative nutritional factors and outcomes after radical cystectomy: A narrative review

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Abstract

Only a few nutritional factors have been identified to predict the risk of developing complications after radical cystectomy (RC). This narrative review delineates the current known effects of preoperative nutritional status factors in this context. The report highlights the heterogeneity between study methods and results. We determined that low albuminemia values increase mortality risk and overall complications. In addition, obesity tends to increase the risk of developing venous thromboembolism and adverse events. Additional prospective studies, using standardized methods to both define and report complications, should be conducted to strengthen the connections between preoperative nutritional status factors and post-RC complications. Furthermore, intervention studies testing the impact of strategies to improve nutritional status on the risk of complications after RC are also needed.

Introduction

Bladder cancer (BCa) is the fifth most commonly diagnosed neoplasm in the U.S.[1] and is one of the cancers with the highest financial burden from diagnosis to death, essentially due to the large number of procedures required for its management.[2] Radical cystectomy (RC) with urinary diversion is the standard surgical treatment for muscle-invasive BCa. The rate of short- and long-term complications after RC remains high despite major improvements in surgical techniques and perioperative subject care.[3,4] While many studies have evaluated improved surgical techniques, no modifiable preoperative nutritional risk factors for post-RC complications have emerged to improve BCa outcomes.[4]

Nutritional status is a confounding factor in a cancer patient's response to surgical stress.[5] The prevalence of malnutrition (nutrition risk score >3)[6] in subjects admitted to the hospital for urological surgery ranges from 20–50%.[7,8] Since nutritional status is a modifiable preoperative factor, subjects could benefit from preoperative nutritional intervention to decrease complications related to cancer surgery.[7,9] Being able to link the risk factor for RC complications with preoperative nutritional status is therefore important in order to better stratify RC-eligible patients.

A growing body of literature has identified preoperative factors associated with complications after RC. We conducted a comprehensive review to determine the current effects of preoperative nutritional status factors on complications after RC.

Methods

Investigators with experience conducting systematic reviews and experts in epidemiology, nutrition, and urological oncology with a particular clinical interest in RC designed the protocol and worked on this comprehensive review.

Research methods

We designed a strategy to identify the association between traditional factors of nutritional status and the risk of complications after RC. We carried out an electronic search of the MEDLINE and EBSCO databases using keywords "cystectomy" and/or "mortality" and/or "complications" and/or "nutritional status" and/or "nutrition" and/or "nutritional" and/or "body mass index (BMI)" and/or "BMI" and /or "albumin" and/or "weight loss." We retained all English language cohort and case-control studies that evaluate at least one preoperative nutritional status factor and the risk of complications or mortality after RC. We included studies published between January 1, 2005 and December 31, 2016, since the quality criteria for reporting surgical complications was introduced in 2002.[10]

A registered dietitian (JA) conducted the first research and analysis of the articles. A urology resident (TBZ) independ-

ently validated the review and also analyzed the articles and quality assessment. Disagreements were resolved by consultation with a third reviewer (VF) to reach a consensus.

Results

We included 40 studies in the review (Supplementary Table 1; available at *cuaj.ca*). Nine studies used at least one of the following standardized methods for reporting complications: Clavien-Dindo,[11] Common Terminology Criteria for Adverse Events 3.0,[12] Memorial Sloan Kettering Cancer Center (MSKCC)[3] classifications. The remaining 31 studies used length of hospital stay, occurrence of any adverse event, specific complication (ileus, delirium, symptomatic venous thromboembolism, parastomal hernia, wound dehiscence), and/or mortality as study outcomes. We found no published randomized trial of nutritional assessment or intervention prior to RC.

1. Standardized method of reporting outcomes

1.1 BMI
Among the nine studies with standardized methods of reporting complications, eight looked at the effect of BMI.[3,13-19] In the Berger et al study,[15] high BMI was associated with a higher risk of developing complications after RC, but not with the mortality rate. Roghmann et al[17] observed that BMI was associated with a higher risk of developing overall complications and high-grade complications. In a multicentre study, Osawa et al[19] reviewed data from 813 patients in Japanese institutions and 1427 patients in U.S. institutions who underwent RC between January 1997 and April 2014. High BMI was associated with a higher 90-day risk of mortality and morbidity. Other studies did not find any association between BMI and RC outcomes.

1.2 Albuminemia
Garg et al also found that low albuminemia concentration was associated with a higher 90-day risk of complications and mortality after RC.[20] In a prospective design, Mursi et al[16] found no difference in complication rate and grade, re-admission rate, and length of hospital stay between the low and normal albuminemia groups.

2. Using the National Surgical Quality Improvement Program (NSQIP) database

2.1 BMI
Five studies examined the association between BMI and RC outcomes using the NSQIP database.[21-25] In the Gandaglia et al study,[21] a BMI >30 kg/m^2 was associated with a higher risk of developing overall complications within 30 day after RC, compared to a BMI <25 kg/m^2. Meyer et al[25] found that subjects with a BMI between 25 and 30 and >30 kg/m^2 were

at higher risk of developing wound dehiscence compared to patients with a BMI <25 kg/m^2. BMI was not associated with RC outcomes in other studies.

2.2 Albuminemia
The association between albuminemia and RC outcomes was assessed in six studies using the NSQIP database.[21-23,25-27] All authors except Meyer et al[25] found an association between low albuminemia (<3.5 g/dl) and a higher risk of complications after RC (early complications, morbidity, and prolonged hospital stay) compared with subjects with albuminemia ≥3.5 or >4.1 g/dl. Albuminemia was not associated with wound dehiscence after RC in Meyer et al.[25]

2.3 Weight loss
Hollenbeck et al[26] observed increased mortality within 90 days after RC in subjects who sustained a weight loss >10% within six months before RC compared to those who sustained no weight loss or a weight loss <10%. Preoperative weight loss of more than 10% was not associated with a prolonged length of hospital stay in this study. In Johnson et al[22] and Lavallée et al,[23] BMI and weight loss ≥10% were not identified as a predictor of complications within 30 days after RC.

3. Non-standardized method of reporting outcomes

3.1 Nutritional score
Jensen et al[28] investigated the association between nutritional risk and length of hospital stay among 246 RC subjects at the MSKCC in New York and the Aarhus University Hospital in Denmark in 2009. Nutritional risk before RC has been assessed by the Subjective Global Assessment Scale[29] at MSKCC and by the Nutrition Risk Screening (NRS)[6] in Denmark. Nutritional risk was not associated with a higher length of stay after RC in this study.

3.2 BMI
Four multicentre studies looked at the association between BMI and RC outcomes.[28,30-32] BMI ≥30 kg/m^2 (vs.<25 kg/m^2) was an independent predictor of overall and cancer-specific mortality.[30] Higher BMI was associated with cancer-specific mortality in patients with soft tissue surgical margin involvement at RC, but the association was not found to be significant using multivariate analysis.[31] BMI was not associated with RC outcomes in the other two studies.

4. Other study designs

4.1 BMI
Twelve studies investigated the association between BMI and RC outcomes.[33-44] Reyes et al[33] found that tract infections, pyelonephritis, wound infections, and overall complications were less frequent in normal-weight patients (18.5–24.9 kg/m^2)

compared to overweight (25–29.9 kg/m²) and obese (≥30.0 kg/m²) patients. BMI was not a predictor of mortality and complication development after RC in the Maurer et al study,[35] except for postoperative bleeding, which was more frequent in subjects with a high BMI. Compared to subjects with a BMI of 18–25 kg/m², subjects with a BMI >30 kg/m² had a higher risk of cancer-specific mortality,[38,42] incisional hernia,[40] readmission 30 and 90 days after RC,[39] ileus,[36] parastomal hernia,[45] and deep venous thrombosis.[43,44]

Psutka et al[41] investigated the impact of BMI and fat mass index on mortality after RC at the Mayo Clinic in Minnesota in 515 RC subjects from 2000–2008. Higher BMI was associated with improved overall survival, while fat mass index was not. Butt et al[34] found no association between BMI and complication rates in 51 consecutive subjects of robot-assisted RC. With a participation rate of 45%, Large et al[37] found no difference between the BMI of subjects who did or did not develop delirium after RC in 91 subjects.

4.2 Nutritional score
Gregg et al[46] defined nutritional deficiency before RC as the presence of one or more of the following factors: albuminemia <3.5 g/dl, BMI <18.5 kg/m², or preoperative weight loss <5%. In comparison with subjects who had a normal nutritional status, defined as the absence of the same three factors, nutritional deficiency was a predictor of mortality within 90 days after RC.

4.3 Albuminemia
Low albuminemia was associated with a higher risk of parastomal hernia,[45] mortality within 90 days after RC,[47-50] a longer hospital stay or re-admission before 90 days after RC,[48] and a higher prevalence of complications after RC.[48]

Liu et al[51] reported that a low serum albumin/(total protein–albumin) ratio has been correlated with tumour progression. A ratio ≥1.6 was associated with a lower risk of cancer-specific mortality after RC in this cohort.

Discussion

The reporting of postoperative complications has improved[10] in the era of modern surgical techniques and perioperative support (2002). For this reason, we conducted a review of publications involving nutritional evaluation and RC complications. In the 40 publications, albuminemia and BMI were the two major nutritional factors reported (Table 1). Even though albuminemia is no longer considered a marker of nutritional status, it has been shown to be associated with poor outcomes after RC. It has been suggested that low preoperative albuminemia increases the risk of mortality and complications after RC. Obesity (BMI >30 kg/m²) also seemed to increase the risk of developing venous thromboembolism and adverse events after RC.

Table 1. RC outcomes associated with serum albumin and BMI

Nutritional factor	Outcome
Serum albumin	
Low	- Mortality (late>early) (7 studies) - Overall complications (late and early) (6 studies) - Longer hospitalization (1 study) - Parastomal hernia (1 study)
BMI	
Low	- Mortality (1 study)
High	- Adverse events (5 studies) - Cancer-specific mortality (1 study) - Deep venous thrombosis (2 studies) - Ileus (1 study) - Improved survival (1 study) - Incisional hernia (1 study) - Mortality (3 studies) - Operative time (1 study) - Parastomal hernia (1 study) - Postoperative bleeding (1 study) - Readmission rate (1 study) - Urinary tract infection/pyelonephritis/wound infection (neobladder reconstruction) (1 study) - Wound dehiscence (1 study)

BMI: body mass index; RC: radical cystectomy.

Disparities between statistical methods, the accuracy of reporting, and the definition of preoperative factors and/or surgical outcomes are important limitations for cross-study comparisons. Due to the wide heterogeneity of study designs and methods used in assessing nutritional status and complications, it is difficult to identify other nutritional factors associated with RC complications.

More than 10 years after the landmark paper published by Martin et al,[10] disparities in the reporting of postoperative urological oncology complications still occur in the literature.[52] Partly based on recommendations in the Martin et al study,[10] a 2007 report by Donat strongly recommended the use of both standardized severity grading scale and a category classification method for reporting complications after RC.[52] In the present review, 31 studies did not use a standardized complication-reporting tool, indicating significant ongoing disparities in the literature today.

Studies were mainly conducted using institutional and national databases and were not designed to investigate the impact of nutritional status on RC outcomes. Retrospective studies have the advantage of less costly access to a larger potential sample size compared to prospective studies, but with an increased risk of selection bias. More than 80% accrued nutritional data retrospectively, similar to the 87% reported in 2007.[52] Psutka et al[41] conducted sensibility analysis to test for possible bias introduced by the exclusion of patients with missing data, but this was unfortunately not discussed in the majority of the literature reported here.

Many studies also observed the impact of BMI on complications and mortality after RC using regression models. Since U-shaped associations are common for BMI and surgery outcomes and mortality,[53] the log-linear relationship between the independent variable (BMI) and the dependent variable (complication) should be confirmed before regression modelling. It is often not stated whether this was verified.[14,15,17-19,22,28,31,35,36,39,41,44,45] Other researchers modelled BMI as categorized variables (>30 vs. ≤30 kg/m^2,[3,24,30,40,43] ≥35 vs.<25 kg/m^2,[23] ≥22 vs.<22 kg/m^2,[42] or in more than two groups[21,25,33,38]).

Despite the validity of NRS for assessing nutritional status in clinical practice,[54] NRS[6] was used in only two studies, with a sample size of 76 subjects each. Further studies are needed to determine whether the NRS can stratify the risk of complications after RC. Most of the studies assessed nutritional status by one single factor, such as BMI or albuminemia. Despite increasing evidence that serum proteins like albumin are not specific indicators of nutritional status,[55] it is still used as a single factor to assess it and to measure the impact of nutritional interventions. Serum protein concentration does not depend on nutritional status alone, but on many other additional factors,[55] such as inflammation or hydration. More comprehensive nutritional scores that involve multiple criteria will likely better define nutritional status and risk-stratify subjects more accurately.

Complications after RC are frequent, with over 67% of subjects developing one or several complications.[3] Some papers used a statistical test instead of (or in addition to) a regression model,[13,15,16,20,24,25,32-37,49] which does not consider the effect of potential confounders. Regression models that consider a time-dependant complication count, specific to each patient, as well as the types of complication, would be more accurate in assessing outcomes after RC.

The weaknesses of the studies stem mainly from the retrospective study design, lack of control for potential confounders, and non-standardized data collection methods for nutritional status and complications after RC. Thus, to move this field forward, it is important to conduct more prospective studies that use standardized methods to define nutritional status before RC and report well-defined, well-classified complications after RC. For example, the measurement of sarcopenia using computed tomography scan or the assessment of frailty using grip strength are now used to define nutritional status in elderly subjects.[56] The European Society for Clinical Nutrition and Metabolism recently published the validation of their diagnostic criteria for malnutrition tool in hospitalized patients.[57] To the best of our knowledge, no published randomized controlled trial has observed the impact of preoperative optimization of nutritional status on post-RC outcomes. Few studies observed a positive impact of the introduction of an enhanced recovery after surgery (ERAS) protocol on RC outcomes; however, ERAS protocols typically only optimize short-term nutritional factors before surgery using an immediate preoperative carbohydrate loading.[58,59] Those protocols are designed to accelerate postoperative recovery, not improve the overall nutritional status of a patient.

Conclusion

A significant effort has been made in the last 10 years for RC surgical amelioration. The high risk of selection bias in retrospective studies, heterogeneity among methods, and the use of a single factor to assess nutritional status make it difficult to predict complications after RC. Low albuminemia tends to increase the risk of mortality and overall complications, while obesity (BMI >30 kg/m^2) appears to increase the risk of developing venous thromboembolism and adverse events after RC. No other factor has been associated with the risk of mortality and complications after RC. Prospective studies with a larger sample size are needed to determine the capacity of standardized tools to assess nutritional status and identify subjects at high risk of complications after RC. In addition, further studies are required and justified to determine the impact of preoperative nutritional status improvement on risk of complications and other outcomes after RC.

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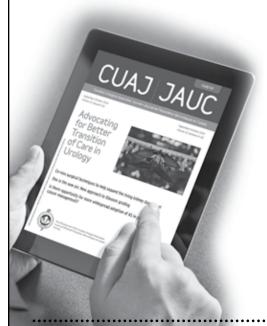
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To answer the three multiple-choice questions associated with this review article, go to: https://www.qzzr.com/c/quiz/453056/claim-section-3-self-assessment-credits-for-reading-cuaj-12-17

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