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Optimizing Nutrition Prior to Radical Cystectomy

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Abstract

Purpose of Review—Malnutrition is a prevalent problem in patients undergoing radical cystectomy. Preoperative malnutrition has been shown to contribute to increased rates of postoperative complications. Given the significant morbidity and mortality of the procedure of radical cystectomy, there is potential for improvement in patient outcomes by nutritional intervention.

Recent Findings—Prospective studies have demonstrated a reduction in postoperative infection rates in patients who receive supplemental immunonutrition prior to major surgery including radical cystectomy. These initial evaluations of nutritional optimization show significant potential for improved outcomes. Additionally, several studies using enhanced recovery after surgery protocols, which include a preoperative nutritional component, have shown a benefit in reducing length of stay.

Summary—Emerging literature has shown the benefits of preoperative immunonutrition in improving postoperative outcomes of radical cystectomy. However, further work is needed to determine the best mechanism to optimize nutrition prior to radical cystectomy.

Keywords

Nutrition; Malnutrition; Bladder cancer; Cystectomy

Introduction

It is estimated that there will be 81,190 new cases of bladder cancer diagnosed in 2018 in the USA, and approximately 25% of these cases will present as muscle invasive disease, which has a high risk of metastasis and is life-threatening [1, 2]. The gold standard for the surgical treatment of muscle invasive bladder cancer is neoadjuvant chemotherapy followed by radical cystectomy (RC). However, this treatment paradigm can be challenging for the patient. Despite being the standard management for muscle invasive disease and a relatively

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

common urologic procedure, complications from RC are exceedingly common [3]. The existing literature shows that up to 66% of patients undergoing RC will suffer a complication within 90 days of surgery, with as much as 25% of these patients suffering from major complication [4, 5].

Bladder cancer is a catabolic disease and malnutrition has been identified as a potential contributing risk factor for postoperative complications after RC. Institutional series have identified that malnutrition is common in the surgical population [6•]. The prevalence of malnutrition in these patients ranges widely (16–55%), which is likely due to various definitions of malnutrition being used between the differing studies [7–9]. Previous reports in urology have focused on the prevalence and impact of malnutrition on cystectomy patients. In addition, recognizing malnutrition is merely the first step in potentially improving outcomes in patients preparing to undergo RC [10•]. One potential way to improve outcomes in patients with malnutrition is to optimize their nutrition status prior to RC, and this review focuses on the existing literature regarding optimization of nutrition prior to RC [11]. Given the relatively limited amount of data specific to the radical cystectomy population, some attention is also given to the literature supporting nutritional optimization prior to major general surgery cases.

Materials and Methods

A Pubmed search was conducted to identify publications related to malnutrition and radical cystectomy in the management of bladder cancer. While emphasis was placed on articles from the past 5 years, historical articles were included as well, to provide additional context to the topic. Key search terms included combinations of “malnutrition,” “radical cystectomy,” “complications,” “bladder cancer,” “urothelial cell carcinoma,” “nutrition,” “oral supplements,” “immunonutrition,” and “Enhanced Recovery After Surgery.”

Malnutrition

Malnutrition has been recognized as a problem in the care of hospitalized patients. In 1974, malnutrition was described in the literature as “the skeleton in the hospital closet” due to its lack of attention in the healthcare system treating the malnourished patients in question [12]. Nevertheless, for many of the years since, malnutrition remained underreported and underrecognized [13]. In 1996, the Joint Commission on Accreditation of Healthcare Organizations mandated that all patients undergo a nutritional screening within 24 h of an inpatient hospital admission. Regrettably, the nationwide adoption of this mandate was slow. To improve the identification of malnutrition, in 2012, the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN) released a consensus statement to standardize the identification and documentation of malnutrition. This statement defined malnutrition as being the presence of at least two of the six following criteria: unintentional weight loss, evidence of inadequate intake, muscle loss, subcutaneous fat loss, fluid accumulation, and diminished functional status as demonstrated by handgrip strength [14•]. After releasing this statement, the Academy of Nutrition and Dietetics and other stakeholders began to work on a Malnutrition Quality Improvement Initiative, which was aimed at improving the quality of care for patients with MN [15].

After the Academy/ASPEN consensus statement was released in 2012, we began a program at the University of Iowa Department of Urology to increase the recognition of malnutrition and improve the quality of care provided to our radical cystectomy patients. We found that when performing an inpatient dietitian evaluation on the patient in the immediate aftermath of a major surgery, the accuracy of nutritional assessment was suboptimal. Patients were unable to provide us with the correct information related to their nutritional status and furthermore, we found that the combination of postoperative pain and pain control medications rendered the measurement of handgrip strength to be particularly difficult to evaluate in post-RC patients. To address these challenges, we added a registered dietitian into our preoperative cystectomy evaluations. This addition has allowed for an accelerated, maximally accurate nutritional evaluation to be performed for all of our RC patients, and the results of these evaluations are documented in the electronic medical record and made available to the entire care team. In addition, preoperative nutritional counseling by a dietitian allows optimization of preoperative nutrition. Our patients still undergo the postoperative inpatient nutrition assessment, but our preoperative assessment has been quite valuable.

Preoperative Immunonutrition

Immunonutrition is nutritional support aimed at improving the body's immune system. Initial attempts to evaluate the impact of nutritional interventions prior to RC have focused on immunonutrition with supplementation of arginine, stemming from data supporting its use in the gastrointestinal cancer general surgery literature [16–18]. Specifically, a landmark prospectively enrolled, randomized controlled trial was performed by Braga et al., in patients undergoing resection for colorectal cancer. In this study, 200 patients were split into two groups, with one group receiving arginine-containing immunonutrition and the other group not receiving immunonutrition. The rate of postoperative infections was 11% in those receiving immunonutrition, compared to 31% in those receiving immunonutrition perioperatively ($p < 0.04$) [18]. After the publication of additional studies, a large systematic review of 35 studies in the general surgery literature was performed by Drover et al. in 2011. They found that perioperative arginine reduced the rate of postoperative infections (OR 0.59 [95% CI 0.50–0.70], $p < 0.0001$) and decreased the mean length of hospital stay (OR – 2.38 [95% CI – 3.39 to – 1.36], $p < 0.0001$) [16].

In follow-up to this extensive general surgery review, three studies were published in the RC population (Table 1). The first publication was by Bertrand et al. in 2014 compared patients who received three doses of arginine-containing formula per day in the 7 days prior to RC, to patients who did not receive any supplement prior to surgery. They found that the patients that received immunonutrition had an overall postoperative complication rate of 40% compared to 76.7% for those who had not received immunonutrition ($p = 0.008$). The specific reductions in complications that were observed were the rates of paralytic ileus on postoperative day seven ($p = 0.02$) and of postoperative infections ($p = 0.008$). The decrease in infections was largely due to the decreased rate of pyelonephritis ($p = 0.03$). In addition to having less overall complications, the Clavien-Dindo complication rate of the study group was also lower than that of the control group ($p = 0.04$) [19]. While its data was promising, this study had its limitations. It was not a true prospective study, since the control group was

obtained from patients undergoing RC immediately prior to the time of the study. These patients were not contemporarily compared, so it is possible that other factors may have impacted their operative performance and confounded the results [19].

The first true prospective randomized controlled trial of immunonutrition in RC patients was performed by Hamilton-Reeves et al. and published in 2015. Patients undergoing RC who received a nutritional supplement containing arginine were compared to patients who received a nutritional supplement without arginine. This trial compared 14 patients in the intervention group to 15 patients in the control group. Both groups of patients received 5 days of their supplement before and after surgery. Patients receiving the arginine-containing supplement experienced a 39% reduction in late postoperative infections ($p = 0.027$) [20••].

The possible biochemical link between improved immune function in patients who receive arginine prior to surgery has been described. It is known that major surgery disrupts the Th1-Th2 balance among T cells, which impairs cell-mediated immunity and makes patients more susceptible to infection [21]. This disrupted balance between Th1 and Th2 T cells is thought to be due to the influence of IL-6, which is most well-known for its effects as a pro-inflammatory cytokine. In the Hamilton-Reeves study, the levels of Th1, Th2, and IL-6 were all measured on follow-up analysis of the two experimental groups. In the patients that received the arginine-containing supplement, the balance of Th1-Th2 T cells was maintained at the time of surgery, and for those who received the non-arginine-containing supplement, it was not maintained ($p = 0.027$). In addition, the plasma concentration of IL-6 was significantly lower in patients receiving immunonutrition supplementation ($p = 0.020$), suggesting that this intervention counteracts the disrupted Th1-Th2 balance and pro-inflammatory response after radical cystectomy [20••, 22••].

The Hamilton-Reeves study also identified that the patients who received arginine-containing supplementation had significantly fewer Myeloid-Derived Suppressor Cells (MDSCs) than did their non-arginine-receiving counterparts. MDSCs are cells which, under normal conditions, rapidly expand upon physical injury and are known to inhibit T-cell responses. This inhibited T cell response lowers resistance to infection by depleting serum arginine through arginase-1, which is found within MDSCs [23]. Furthermore, T lymphocytes are dependent on arginine for their proliferation, so these findings suggest that there are multiple mechanisms for infection prevention when patients receive supplemental arginine [20••, 24].

In contrast to the benefits demonstrated in the Bertrand and Hamilton-Reeves studies, the third study conducted of immunonutrition in RC patients did not identify a benefit of immunonutrition. Published by Lyon et al. in 2017, 40 patients undergoing RC were provided with 5 days of arginine-containing immunonutrition prior to surgery. These patients were compared to a control group of 104 patients who underwent RC prior to the study period, and who did not receive immunonutrition. No differences were observed between the 90-day postoperative complication rates of the two groups. The authors noted that the study was only powered to detect a 25% reduction in infection rates and was underpowered to find differences smaller than this. Further, the control group in this study had a relatively low infection rate (32%), which may reflect other favorable hospital

practices and confound their results [25]. Moreover, similarly to the Bertrand et al. study, this study is limited in that the control group consisted of prior patients so it is possible that other hospital practices may have changed, which may have reduced the benefit of the immunonutrition.

In response to general surgery literature along with the subsequent urologic literature on immunonutrition, the University of Iowa Department of Urology began supplementing all patients undergoing RC with arginine-containing immunonutrition (commercially available products include Impact Advanced Recovery from Nestle or Ensure Surgery Immunonutrition from Abbott). This is to be taken three times daily, in the 5 days immediately prior to RC. All patients are provided with verbal and written dietary instructions at the preoperative clinic visit from a registered dietitian, and these instructions include the recommendation of a high-calorie, high-protein diet before and after surgery once tolerating a general diet. Patients are provided with nutritional information and suggestions for potential ways to achieve this high-protein diet.

Carbohydrate Loading

Compared to supplementation with arginine-containing nutritional formula, the literature on optimization of preoperative carbohydrate nutrition prior to RC is less robust. It has been hypothesized that “nothing by mouth” prior to surgery leads to a period of preoperative fasting, which can promote insulin resistance and lead to an intensified catabolic state in postoperative RC patients [26, 27]. Therefore, in the general surgery literature, the role of preoperative carbohydrate loading has been examined [28]. While oral carbohydrate supplementation has been demonstrated to be safe and effective in lowering insulin resistance, an improvement in postoperative outcomes has not been clearly demonstrated [28]. Given the low risks of implementation, at the University of Iowa, we do encourage patients to perform carbohydrate loading prior to surgery.

ERAS Protocols

Significant literature is available that supports the use of Enhanced Recovery After Surgery (ERAS) protocols after RC [29–31]. Some of these studies mention “preoperative optimization,” which typically includes recommendations to patients that they eat a high-protein or high-carbohydrate diet prior to surgery [30, 31]. However, the details of nutritional interventions within ERAS studies are often not explicitly stated. Further work is needed to identify which portions of ERAS protocols are most significantly contributing to improved outcomes. At the University of Iowa, we have an ERAS protocol which incorporates aspects including monitoring of total amount of IV fluids administered, encouragement of early ambulation, and the early feeding.

Conclusions

The need for preoperative nutritional optimization has been broadly demonstrated through the identification of high rates of malnutrition among patients scheduled to undergo RC and, more importantly, through increased rates of post-surgical complication among these

malnourished patients. Studies are emerging that highlight the advantageous effects of nutritional optimization with immunonutrition prior to RC. Current data supporting the use of preoperative immunonutrition is promising, but largely based on two small studies [19, 22]. Additional data is needed, and particularly from larger prospective trials with enough power to detect more modest differences in complication rates between patients with different nutritional optimization prior to surgery. Despite the current limitations in the existing literature, this is an exciting area primed for significant research and potential future nutritional-based interventions to improve the outcomes of RC.

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Table 1

Summary of studies on preoperative immunonutrition in radical cystectomy patients

Year	Author	Number of patients	Intervention group	Duration of intervention	Control group	Results
2014	Bertrand	60 (30 each group)	Impact Advanced Recovery	7 days prior to surgery	Obtained from hospital database	Reduced complications Reduced infections
2015	Hamilton-Reeves	29 (14 in intervention group)	Impact Advanced Recovery	5 days before and after surgery	Nutrition Supplement Boost Plus	Reduced intraabdominal infections
2017	Lyon	144 (40 in intervention group)	Impact Advanced Recovery	5 days prior to surgery	Obtained from hospital database	No differences in postoperative complication rates